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THE PATHOLOGIC PHYSIOLOGY OF PROTEOLYTIC ENZYME-INDUCED PERITONITIS

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AN IMMEDIATE and violent reaction of the serous enclosure followed by bacterial invasion and its consequences is the early effect of gastrointestinal content contamination of the peritoneal cavity. The following study concerns the first aspect of the process.

Hydrochloric acid and pepsin cause chemical irritation of the peritoneum when pure gastric juice enters the peritoneal cavity. Beyond the pylorus, trypsin and lipase constitute the most deleterious factors. Contamination by gastric contents alone is better tolerated than that by intestinal secretions since bacteremia is more likely to be associated with the latter. The efficiency of the body in combating the peritoneal assault by the gastric and the enteric proteolytic systems is another point of inquiry. An understanding of the defense mechanisms involved and the therapeutic principles deduced from such a study should be helpful in dealing with these acute abdominal emergencies.

MATERIAL AND METHODS

Albino rats weighing approximately 100 grams were injected intraperitoneally with gastric juice, pepsin, trypsin, and a fecal eluent. The gastric juice was obtained by nasogastric suction from postoperative patients, and was filtered through a coarse, crepe-surfaced filter paper. The feces were blended in a 1:2 ratio with pH 7.5 citrate-phosphate buffer, and the supernate was used after centrifugation. Pepsin* and trypsin† were dissolved in 0.25 N HCl and pH 7.5 citrate-phosphate buffer, respectively. Parallel experiments were conducted in duplicate with the crystalline and the natural proteolytic enzymes.

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*Pepsin 3X crystallized, Pentex Incorporated, Kankakee, Ill.

†Trypsin, Parenzyme Aqueous, National Drug Co., Philadelphia, Pa.

In the first series, 6 rats were injected intraperitoneally with 10 ml. of gastric juice, and 6 with 10 ml. of a fecal eluent. The animals were sacrificed at intervals of 15 to 80 minutes. In the second series of 12 rats, 25 mg. of pepsin or 2,500 U. of trypsin in 5 ml. of the appropriate diluents (as mentioned above) were used. The pH of the peritoneal fluid was determined and the proteolytic activity of a 1.0 ml. sample analyzed. The procedure employed for proteolytic activity determination was previously reported.[1, 4] Additional enzymatic activity after acidification to the initial pH of 1.2 with 0.25 N HCl was determined in rats which received intraperitoneal injections of gastric juice and pepsin.

Five to ten minutes prior to intraperitoneal administration of 100 mg. of pepsin in 5 ml. of 0.25 N HCl, 6 rats were injected intraperitoneally with 5 ml. of plasma, and 6 with 5 ml. of saline. Comparison of the proteolytic activity of 1 ml. of the pepsin solution in plasma with that in saline was made prior to injection. The proteolytic effect of 1 ml. of the peritoneal contents was determined at 15, 30, and 80 minutes.

The effect of intraperitoneal administration of plasma on the inhibition of intraperitoneally injected trypsin was studied. The proteolytic effect of a solution of 5,000 units of trypsin in 5 ml. pH 7.5 citrate-phosphate buffer diluted with 5 ml. water and with 5 ml. plasma was determined. Six rats were injected intraperitoneally with 5 ml. of water and 6 rats with 5 ml. of plasma, prior to the administration of 5,000 units of trypsin in 5 ml. pH 7.5 citrate-phosphate buffer. The animals were sacrificed at 15, 30, and 80 minutes, and the proteolytic effect of 1 ml. of peritoneal content was determined. Similar studies were performed in 12 rats, employing 5 ml. gastric juice and 5 ml. fecal eluent.

RESULTS

The gastric juice employed had a pH of 1.2 initially but, upon intraperitoneal injection, rapid buffering occurred. Accompanying the change of pH was an immediate drop in proteolytic activity. However, upon reacidification of the inactive peritoneal material to the original pH of 1.2, a return of enzymatic activity to the original level was noted (Fig. 1).

The pH of the fecal eluent was 6.7 prior to intraperitoneal injection and remained at 6.7-7.1 during the period of the experiment. Prior to the intraperitoneal injection, 1 ml. of the material digested 41.1 per cent of the substrate. Fecal proteolytic activity was depressed in the peritoneal cavity at a slower rate than that of gastric juice. Fifteen and eighty minutes after intraperitoneal incubation of gastric juice, the peptic activity was depressed to 44.5 per cent and 7.2 per cent of the initial value and when feces were employed 80 per cent and 58 per cent of the initial proteolytic activity persisted. Thus, under similar circumstances, the inhibitory action of the peritoneal cavity on fecal proteolytic activity was not as effective as it was on gastric juice.

The inhibition of the proteolytic activity of gastric juice and pepsin was similar to that of fecal eluent and trypsin, although the magnitude differed (Figs. 1-3). The pepsin-HCl solution was neutralized within 15 minutes. However, upon reacidification, the return of proteolytic activity was not as marked as in the case of gastric juice.

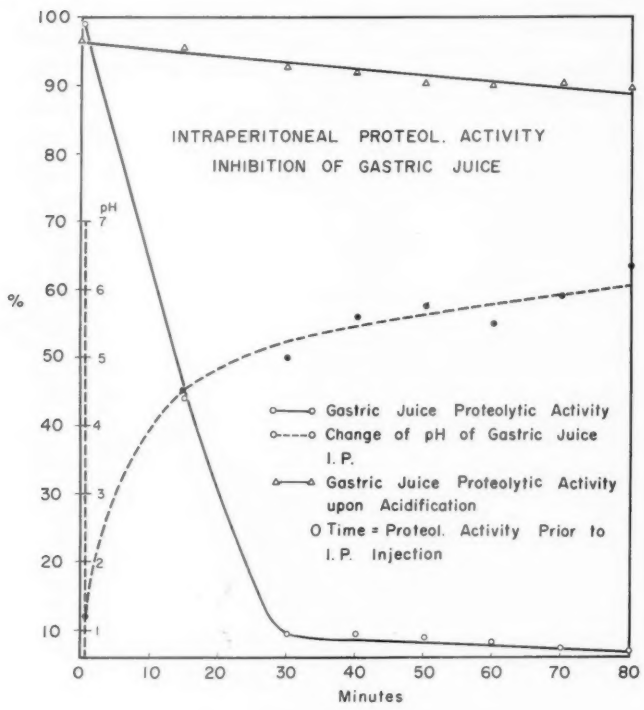
INTRAPERITONEAL PROTEOL. ACTIVITY
INHIBITION OF GASTRIC JUICE
pH
%
Minutes
Gastric Juice Proteolytic Activity
Change of pH of Gastric Juice I. P.
Gastric Juice Proteolytic Activity upon Acidification
O Time = Proteol. Activity Prior to I. P. Injection

Fig. 1

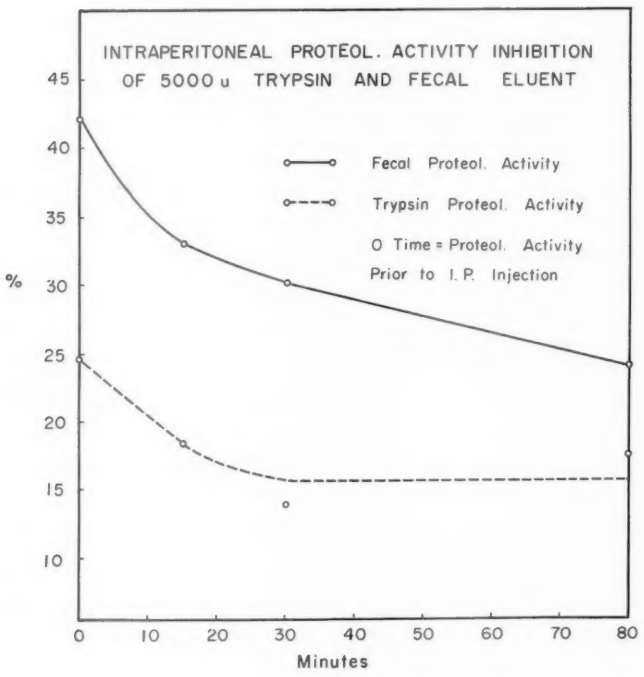
INTRAPERITONEAL PROTEOL. ACTIVITY INHIBITION
OF 5000 u TRYPSIN AND FECAL ELUENT
%
Minutes
Fecal Proteol. Activity
Trypsin Proteol. Activity
O Time = Proteol. Activity
Prior to I. P. Injection

Fig. 2.

No additional neutralizing effect of intraperitoneal plasma on the peptic activity of gastric juice or of crystalline pepsin injected intraperitoneally was noted. The inhibition was caused by buffering for, upon acidification, proteolytic activity returned to the same levels as that of the control animals.

The intraperitoneal administration of plasma in rats that had been injected with crystalline trypsin or fecal eluent completely inhibited proteolytic activity (Fig. 4).

DISCUSSION

The rapid inhibition of the peptic activity of gastric juice and pepsin-HCl solution upon intraperitoneal injection was associated with the buffering of the material injected. Peptic activity increased upon reacidification to the initial pH of 1.2 regardless of whether gastric juice or pepsin-HCl was administered. The gastric juice peptic activity returned to the initial values. However, only a fraction of the initial proteolytic activity was detected when crystalline pepsin was used. This difference may well be due to a pepsin-protective constituent of the gastric juice.

In the case of trypsin and fecal proteolytic activity, the pH remained as anticipated at levels optimal for this enzyme. The antitryptic effect was explained by dilution and an antiproteolytic effect of protein-containing peritoneal exudate.

Albumin, hemoglobin, casein, and the protein components of plasma are active inhibitors of peptic and tryptic proteolytic activity in vitro.[1] Peritoneal exudation of protein as a defense mechanism to pepsin-HCl and trypsin soilage of the peritoneal cavity must be considered. In the former type of soilage, it is caused primarily by buffering; in the latter, it is the result of an active process of enzyme inhibition.

Whipple[6] and Wangensteen[5] suggested that the exudate which forms in the peritoneal cavity in experimental pancreatitis is part of the defense mechanism. Both authors suggested the protective value of such exudates in dogs with experimental pancreatitis and in acute hemorrhagic pancreatitis in humans. The sudden intraperitoneal efflux of antitryptic materials may be a primary defense mechanism against tryptic proteolytic contamination of the peritoneal cavity. The conditions under which protein escapes into the peritoneal cavity have been discussed by Courtice.[2, 3] Protein concentrations of the peritoneal fluid of less than equilibrium values cause a protein efflux into the peritoneal cavity, while water and electrolytes are absorbed. In addition, the irritative effect of gastrointestinal contents in the peritoneal cavity will cause an increased capillary permeability to protein.

Since pepsin in the gastric juice or in crystalline form is active at an acid pH, buffering will cause neutralization of its proteolytic effect. A direct antipeptic effect, therefore, even if present, would be of no great significance. Neutralization of the peritoneal contents using either a weak alkaline buffer or plasma should be appropriate therapeutically in peritonitis caused by gastric juice.

Contamination of the peritoneal cavity by pancreatic secretions or postpyloric intestinal contents should be even more effectively combated by instillation of proteolytic substrate into the peritoneal cavity in excess of that normally

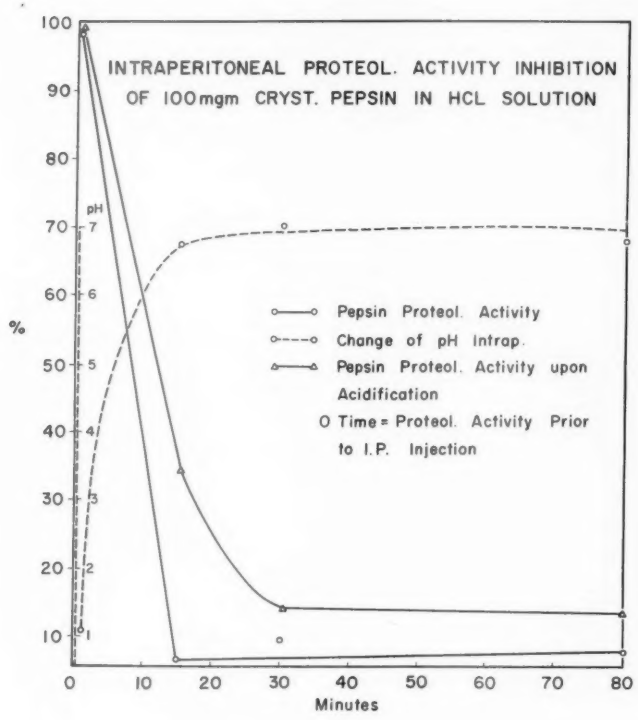
INTRAPERITONEAL PROTEOL. ACTIVITY INHIBITION
OF 100mgm CRYST. PEPSIN IN HCL SOLUTION
pH
%
Pepsin Proteol. Activity
Change of pH Intrap.
Pepsin Proteol. Activity upon Acidification
O Time = Proteol. Activity Prior to I.P. Injection
Minutes

Fig. 3.

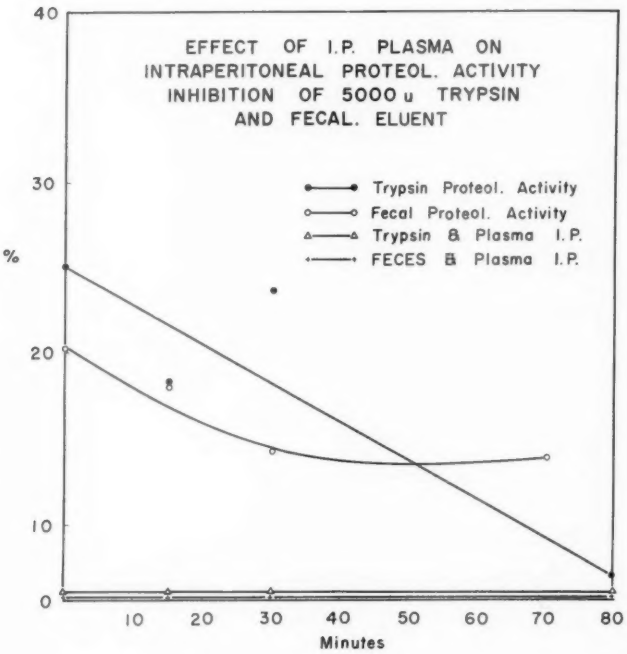
EFFECT OF I.P. PLASMA ON
INTRAPERITONEAL PROTEOL. ACTIVITY
INHIBITION OF 5000 u TRYPSIN
AND FECAL. ELUENT
Trypsin Proteol. Activity
Fecal Proteol. Activity
Trypsin & Plasma I.P.
FECES & Plasma I.P.
%
Minutes

Fig. 4.

produced under such circumstances. Intraperitoneal administration of plasma in pancreatitis was suggested in 1913 by Whipple. In addition to having a beneficial antitryptic effect, intraperitoneal protein should plug the capillary sieve, limit the protein losses, and create a reservoir for absorption into the vascular system via the lymphatics.

SUMMARY

Inhibition of gastric juice, feces, trypsin, and pepsin proteolytic activity following their intraperitoneal injection was studied in experiments on rats. Buffering of the acid gastric juice and pepsin solvent was found to be the principal manner of neutralization of peptic activity. Physiologic inhibition of the tryptic activity of feces and crystalline trypsin was found to occur but at a slower rate. This was accelerated by intraperitoneal injection of plasma. Antitryptic activity of peritoneal protein-rich exudate is thought to be the important cause of trypsin inhibition in pancreatitis. The possible approaches to treatment of conditions such as enteric ruptures and pancreatitis, usually associated with spillage of proteolytic-containing materials into the peritoneal cavity, are discussed.

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DEVELOPMENT OF A NEW FIBRINOLYTIC ENZYME AND ITS USE IN SURGICAL LESIONS

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DURING the past 10 years, we have assayed the efficacy of a large number of both crude and refined fibrinolytic enzymes.[1, 2, 3] Through our efforts during these years, we have established certain directional criteria rather than final specifications, as we are not yet sure what the end realization will be. These criteria may be listed briefly as follows:

1. The rapid liquefaction of the necrotic elements in the wound.
2. The capacity to free granulation tissue interstices of bacteria and necrotic debris.
3. The reduction of wound inflammation.
4. A material that is nontoxic and nonallergenic to the host and local wound tissues.
5. A vehicle to concomitantly carry and release with the active enzyme a bactericidal concentration of a broad-spectrum antibiotic, in order that: (a) wound soilage with organisms will be decreased; (b) further necrotizing effects on wound healing will be removed; and (c) the outgrowth of resistant strains of organisms and potential ward contamination will be prevented.

New materials are screened not only for substrate spectrum, i.e., collagen, fibrin, pus, and blood clot, but also for compatibility with other enzymes, antibiotics, and vehicles for application. The latter group is especially important as it increases the range of employment in various surgical lesions.

It is always important in discussing enzymes to recall that specificity of both species and tissue is involved. We call the tissue substance upon which the enzyme is most efficient its specific substrate. Some enzymes of a strong proteolytic character have an effect on a number of substrates, while others are extremely limited.[3, 4]

For the past 18 months we have been studying a new bovine blood fibrinolysin derivative, Elase,* that has proved to have great potential. The enzyme comes as a sterile, lyopholized powder, readily soluble in normal saline or distilled water, with a pH of 7.0. It has also been incorporated in a tube with a non–water-soluble jelly that gives it an indefinite storage life and extreme ease of application. The enzyme is compatible with a number of antibiotics and desoxyribonuclease.

This enzyme is specific for fibrin substrates and thus rapidly dissolves fibrinous materials found in serum, clotted blood, and collections of purulent exudate. One of the earliest effects noted with the use of Elase was the rapid removal of

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*Elase supplied by Parke, Davis & Co., Detroit, Mich.

pus and the subsequent decrease in organism flora. When combined with Chloromycetin, the organism flora decreased to spotty contamination or, as in many instances, sterility. Resistant strains have not grown out in this study.

The enzyme permits more rapid epithelial outgrowth on prepared rabbit ears than either saline or placebo treated controls. It has no irritative effects on granulation tissue in wounds, but there is a decrease in the tendency toward hyperproliferation of this wound-filling material. As with many fibrinolytic enzymes, there is a rapid clearing of inflammatory tissue reaction about the wound shortly after application, with a resultant decrease in swelling, redness, tenderness, and pain.

In the use of enzymes in surgery, especially for wound hygiene, much imagination is required in developing a technique of application. Adequate application must meet the following requirements: (1) there must be intimate, prolonged contact between enzyme and substrate interface, (2) on surface wounds, the enzyme must be prevented from drying, and (3) in all wounds the surface must be cleaned or washed daily so that by-products of the enzyme-substrate reaction do not accumulate and thus tend to inhibit further enzyme activity.

To date, we have found Elase in an ointment base to be very useful on surface ulcers, superficial second-degree burns, abscess cavities, wound infections, and sinus tracts.

The enzyme gel is applied in layers over the wound surface and covered with a sheet of petroleum jelly or Adaptic gauze. This is then covered with cotton gauze pad and bound or taped to keep in place.

In deep wounds, abscesses (supdiaphragmatic and empyema), and sinus tracts we have employed rubber catheters inserted into the wound. The powdered Elase is dissolved in normal saline to a final concentration of 3.5 units per cubic centimeter and a 1 per cent concentration of the appropriate antibiotic is added. The enzyme-antibiotic solution is administered as a constant drip of 20 drops per minute or by periodic instillations every 3 to 4 hours of enough solution to wet the overlying dressing.

In the treatment of wounds which have a heavy purulent exudate, we noted that the addition of 600 units of desoxyribonuclease to 1 unit of Elase and 1 per cent concentrations of the appropriate antibiotic were the most efficacious.

All patients on enzyme therapy should receive parenteral antibiotics (if indicated) for rapid control of host invasion and anti-inflammatory agents to reduce tissue reactions. Chloromycetin, neomycin, polymyxin, Albamycin, and penicillin have been compatible with the enzyme. The antibiotic used was selected from pretreatment culture analysis of organism sensitivity.

RESULTS

The clinical appraisal represents the employment of Elase in 125 patients with 175 lesions. Alternate varieties of surgical lesions were treated with Elase, Elase plus desoxyribonuclease, and 1 per cent Chloromycetin or another compatible and appropriate antibiotic. In 90 per cent of the patients selected for therapy, the response was excellent (Table I).

Results were interpreted as *excellent* in those patients with a wound responding in 24 to 72 hours, with not only the removal of necrotic debris, but also a marked reduction in bacterial flora. *Good* was reserved for wounds requiring 72 to 120 hours. All wounds responding under 10 to 12 days, in which saline controls indicated the need for 14 to 20 days, were listed as *fair*. *No effect* was limited to cases in which infected necrotic debris resisted lytic activity. In the last 2 groups there were 9 patients who had third-degree or deep second-degree burn eschars as the basic substrate or similar substrates found in decubitus, arteriosclerotic, and diabetic ischemic ulcerations, and osteomyelitis.

TABLE I. CLINICAL RESULTS OBTAINED ON ELASE THERAPY

LESIONS	NO. OF PATIENTS	RESULTS			
		EXCELLENT	GOOD	FAIR	NO EFFECT
Burns: all types	30	23	4	-	3
Large hematomas	3	3	-	-	-
Large abscesses, wound infections and sinus tracts	52	43	6	1	2
Ulcerations, all types	40	24	13	1	2

Burn Wounds.—Thirty patients with burn wounds of all degrees of tissue destruction were studied. Elase must only be used where the substrate is a serous crust or the wound contains infected granulation tissue (Figs. 1 and 2). Elase has no effect other than wetting on a third-degree burn eschar. It has proved to be equal or superior to the other available fibrinolytic enzymes on crusts and definitely of greater advantage on the infected granulation tissue wound.

Ulcerations.—In this series, 40 patients were studied with stasis, arteriosclerotic, diabetic, and decubitus ulcers. Elase is extremely effective on all ulcers with a purulent exudate as the primary substrate. In ulcers where ischemic collagenous substrates were present, the Elase effect was limited to reducing bacterial flora and diminishing the exudative reaction (Figs. 3 and 4). A proteolytic enzyme and/or surgical débridement were required to rid the wound of the residual denatured collagen.

Wound Infections, Abscesses and Sinus Tracts.—Fifty-two patients were studied in this group. Bacteriology revealed hemolytic *Staphylococcus aureus* and mixed coccal gram-negative organisms as the predominate wound flora. Two patients with empyema cavities were treated with Elase and the appropriate antibiotic through closed thoracotomy drainage tubes. In both cases, the chest cavities were clean after 8 days of daily instillations, with complete re-expansion of the lung. Following a ruptured duodenal stump, cholecystectomies, and hip-pinning procedures intra-abdominal sinus tracts responded in 48 to 96 hours to periodic instillations of Elase with the appropriate antibiotic.

In heavy purulent postoperative wounds and abscess cavities, the addition of desoxyribonuclease seemed to speed up the liquefaction of the purulent exudate. In a number of instances, wounds treated with the 3 elements responded in 12 to 24 hours. Failures occurred as stated above when the primary substrate was denatured collagen.

In 3 patients with large hematomas the daily instillation of Elase rapidly dissolved the clotted elements. In this small series, which included one large retroperitoneal hematoma from a ruptured kidney, approximately 5 days of therapy were required.

Fig. 1.

Fig. 2.

Fig. 1.—Second- and third-degree burn crusts 72 hours after injury when Elase therapy was initiated.

Fig. 2.—Forty-eight hours after start of Elase therapy.

Toxicity.—In no instance was toxicity manifested by either local or systemic signs or symptoms. Local wound erythema rapidly cleared under topical

application and maceration was not found. Toxicity studies included liver, renal, and blood evaluations. There were no signs of local surface organisms invading the lymphatics or blood stream. The instillation of 20 to 50 c.c. of Elase into the chest, abdominal, or retroperitoneal cavities did not provoke a febrile response.

DISCUSSION

The high percentage of excellent results was obtained because of our selection of patients with appropriate wound substrates. Thus, while we tested Elase in wounds with denatured collagen, we were primarily studying its effect on the purulent exudates. Surgeons employing enzymes must be as aware of the nature of the enzymes' substrate specificity as they have become of bacteria sensitivities to antibiotics. Further, enzymes are ancillary tools and do not replace proved surgical techniques. Once a wound surface of considerable size is rid of necrotic and purulent debris, that wound should be closed secondarily or grafted. Topical therapy may be used until wound healing occurs only in abscess cavities, postoperative wound infections of limited extent, and epithelizing burns.

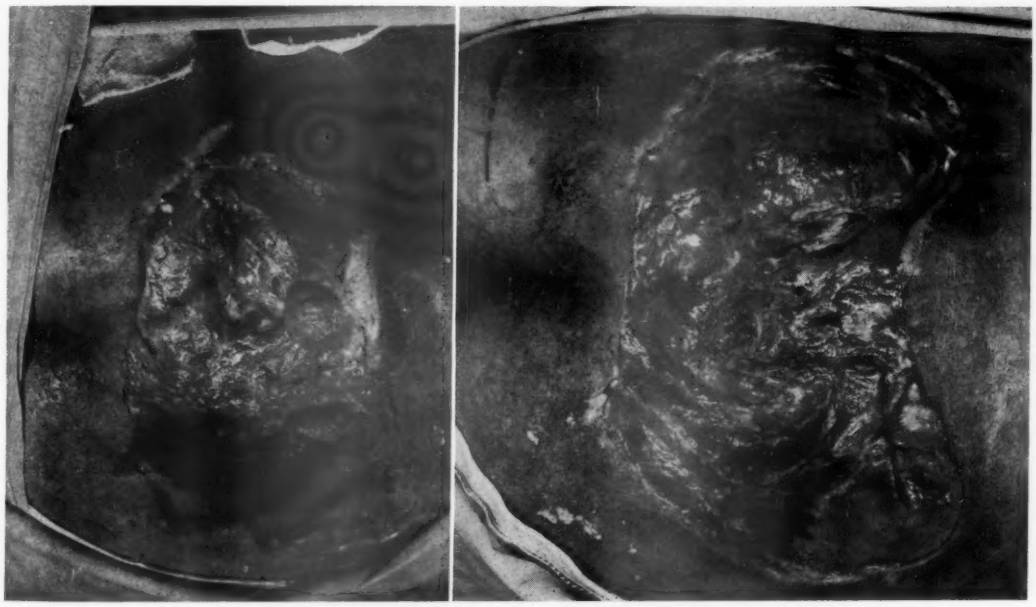
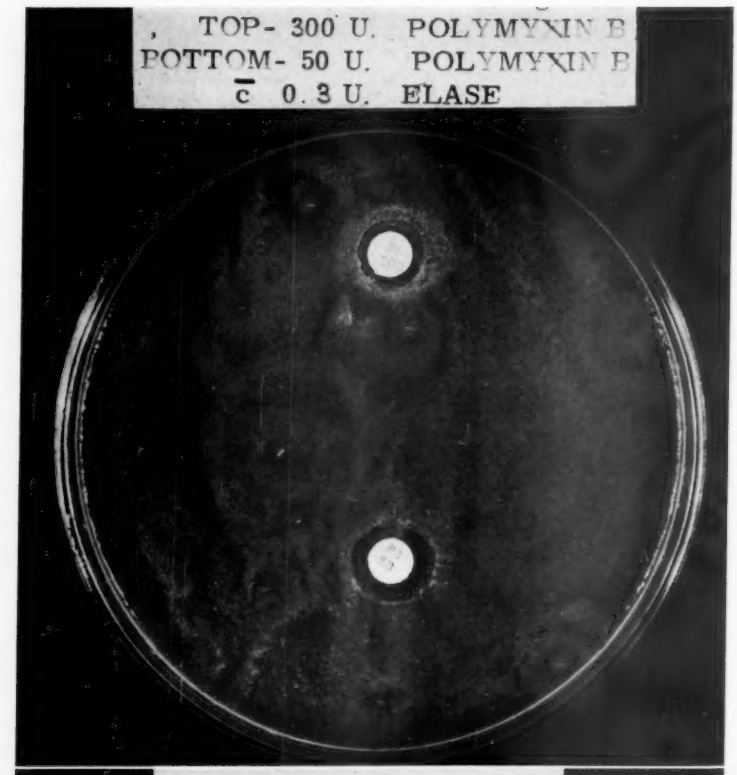


Fig 3. Fig. 4.

Fig. 3.—Large, partially unroofed decubitus ulcer with massive contamination.
Fig. 4.—Five days of Elase therapy markedly reduced bacterial flora and cleaned up all but necrotic collagenous structures.

An interesting and important effect of Elase was noted in bacteriologic studies. In vitro studies indicated that Elase has a bacteriostatic effect on a few strains of wound pathogens. This effect is capricious but Elase has demonstrated a bacteriostatic capacity for exceeding that of any enzyme tested. When combined with a compatible antibiotic, however, there is a definite synergistic effect on a number of resistant wound organisms. This has been shown in a series of in vitro tests where organisms growing in high concentrations of a

Fig. 5.



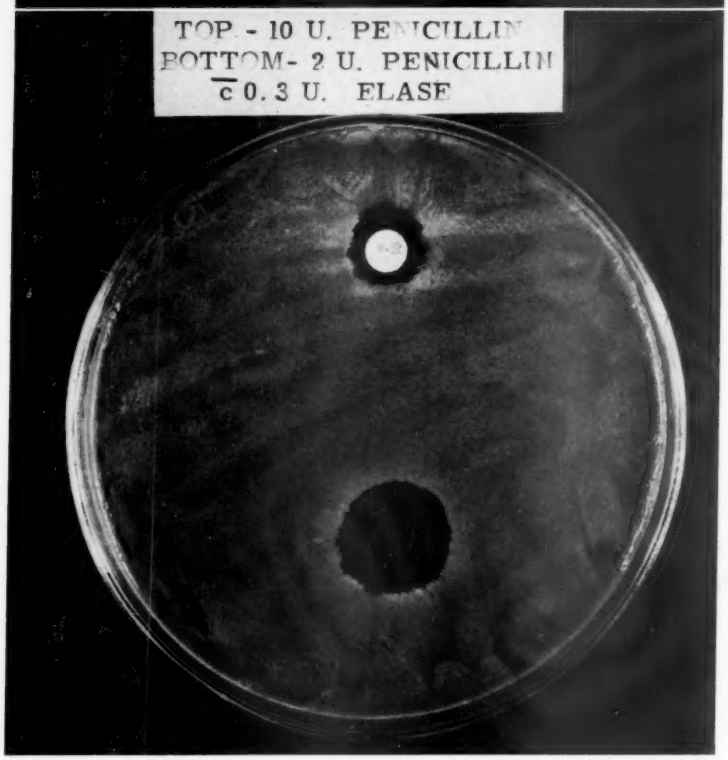


Fig. 6.

Fig. 5.—Example of synergistic action between Elase and polymyxin on resistant Psuedomonas culture from surgical lesion in Fig. 3.

Fig. 6.—Graphic result of synergism between Elase and penicillin on resistant hemolytic *Staphylococcus aureus* from wound culture.

specific antibiotic are reduced to sensitivity in the presence of low concentrations of an antibiotic-Elase solution (Figs. 5 and 6).

This effect has been demonstrated in some of our clinical experiences where pretreatment and periodic cultures, demonstrating resistant organisms, were taken during Elase-antibiotic therapy. In most instances, the purulent exudate was rapidly liquefied and bacterial counts rapidly diminished. In a few instances, the wound surface was completely decontaminated.

In a number of patients with organisms of resistant strains noted prior to therapy, the organisms continued to proliferate during the course of treatment but the exudate was removed, the bacterial count diminished, and skin grafting was successfully carried out. Studies are now in progress exploring this phenomena.

SUMMARY

1. A new fibrinolysin, Elase, has been developed and clinically tested that is extremely active on fibrinopurulent exudates.

2. Elase is compatible with a number of broad-spectrum antibiotics and has, in some instances, demonstrated a synergistic effect that markedly diminishes the proliferation of resistant wound pathogens to the antibiotic.

3. The enzyme has proved its clinical usefulness when applied to appropriate wound substrates.

4. The enzyme is nontoxic when employed topically and in walled-off body cavities.

5. Further studies are in progress.

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RELIEF OF POST-DISCECTOMY PAIN BY SYMPATHECTOMY

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THE continuing or additional symptoms following lumbar nerve root exploration or decompression for herniated nucleus pulposus and spondylolisthesis are very similar to those of patients with causalgia-like states or vascular insufficiency of the extremities. These symptoms, including coldness, numbness, tingling, intermittent claudication-like cramps and resting pain or cramps, have been called "vascular equivalents,"[6] since examination of most of these patients demonstrated no actual vascular disease. Lumbar sympathetic block gave relief of these "vascular equivalents" in many patients; therefore lumbar sympathectomy was performed in selected cases.

The following cases support a concept that some of the manifestations of sciatica associated with herniated nucleus pulposus, or following surgical exploration of the lower nerve roots, are secondary to decreased blood supply of the nerve root subjected to compression, and that early removal of compression may be followed by relief of nerve root ischemia and relief of symptoms. Prolonged nerve root compression may require sympathectomy to relieve ischemia.

CASE REPORTS

CASE 1.—C. Y., a 56-year-old white male, injured his back lifting in a shipyard in 1956 with subsequent mild back pain until 3 months before when he began having aching pain in the right thigh and calf, worse in the morning upon awakening. A diagnosis of "blood clot in the leg" prompted intravenous medication which made him warm all over and gave temporary relief. Five weeks before admission, traction in a hospital had given relief but symptoms returned shortly after traction was discontinued. The patient was admitted complaining of pain in the right thigh and leg, numbness and coldness of the foot. Examination disclosed ¾ inch atrophy of the right thigh compared with the left. The right leg was cooler to touch. The color was comparable bilaterally. Ulnar pulse was obliterated bilaterally and no flushing of hands with Allen's test was seen. Aortic pulsations were normal, femoral pulsations were 4 plus bilaterally, popliteal 2 plus, dorsalis pedis and posterior tibial 2 plus. There was slow return of flush in the feet. Neurological examination showed diminished ankle jerk on the right and a band of sensory diminution from the iliac crest posteriorly down to the ankle and including the big toe. The impression was that there was evidence of mild arteriosclerosis, but that the symptoms were due to a herniated nucleus pulposus at L_5-S_1 level. On Dec. 15, 1958, a herniated nucleus pulposus was removed at the L_5-S_1 level. There was immediate relief of all symptoms of pain, numbness and coldness, and relief has continued.

CASE 2.—R. B., a 48-year-old Negro male, developed pain in the right leg and lower back while pushing a wheelbarrow in July, 1955. He could not work because of the back pain and on Aug. 1, 1955, disc material was removed from L_4-L_5 interspace on the right and a spine fusion was executed. Immediately after operation there was some numbness of the right leg and foot but no loss of motor control. The patient began to complain of coldness

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in the right leg and foot, deep muscle tightness and disturbing numbness of the toes. He suffered cramping in the right calf at night. These complaints continued for 1 year until lumbar sympathetic block was performed on the right with 90 per cent relief of coldness, numbness, and pain for 1 week. Then symptoms returned. Thirty-one months after the original operation, lumbar L_5-S_1 area was explored. A ridge of bone was found, but there was little protruded disc material. Further spinal fusion was executed. The patient's complaints continued and 2 weeks after operation lumbar blocks again were created, again with relief of symptoms. At this time there was diminished pin prick sensation on the side of the leg, dorsum and sole of the foot, and diminished knee jerks. There was no evidence of vascular disease. Lumbar sympathectomy was performed in which L_1, L_2, L_3, and L_4 on the right were removed. Immediately postoperatively the patient's complaints of coldness and numbness were relieved. He has been followed for 11 months with maintenance of relief of symptoms except for pain in the lower back.

CASE 3.—H. L., a 34-year-old white male plumber, fell in November, 1952, with resultant severe pain in the small of the back. Two or three days later he began having cramps in both legs. A spondylolisthesis was found. In April, 1953, a spine fusion was performed. Postoperatively, the left leg still cramped and went to sleep at times. In January, 1954, the patient fell and broke the spine fusion. In February, 1955, a second spine fusion was executed. Two months following this he began noticing symptoms suggestive of intermittent claudication after 8 or 10 blocks of walking, with cramps in both legs and stiffness of the muscles. In June, 1956, a lumbar sympathetic block was created, giving about 75 per cent relief of aching and numbness for 48 hours. Then symptoms gradually recurred. A second block was performed reproducing benefit for about 48 hours. Upon examination, the left foot appeared slightly lighter in color than the right, but there was no difference in skin temperature. Peripheral pulses were full and bounding bilaterally. The left knee jerk was slightly diminished, and there was some diminution of pin prick and light touch on the left in the region of L_3, L_4, and L_5 dermatomes. On Aug. 6, 1956, a left lumbar sympathectomy was performed, removing L_1, L_2, L_3, and L_4 ganglia. The patient was last seen 8 months after operation with no recurrence of leg cramps, pain, or numbness, and he was working.

CASE 4.—H. B., a 50-year-old white female, fell flat on her back in December, 1953, and one week later began having numbness of the left leg and pain in the left hip. She had manipulative treatment and injections without benefit. In January, 1955, spondylolisthesis was found, and the left hemilamina of L_5, which was said to be pressing on the dura mater, was removed. Spine fusion was not performed. Six weeks later spine fusion was carried out, after which pain continued unabated. The patient continued to complain of numbness of the left great toe, pain in the left leg, cramping in the left calf at night, and coldness of the left leg. On May 17, 1956, a left lumbar sympathetic block was created with resultant relief of cramps, numbness, and coldness for 48 hours. On May 6, 1957, a left lumbar sympathectomy was performed in which L_2, L_3, and L_4 ganglia were removed. Postoperatively, the leg cramps and coldness were relieved and numbness was much improved. The patient returned to work 6 weeks after sympathectomy, with numbness of the great toe and leg completely relieved but with a dull ache remaining in the side of the leg and thigh on the left. There was also continuing dullness to pin prick over L_5-S_1 dermatomes. Since the patient continued to have pain in the left leg with slight recurrence of numbness, decompression of the nerve roots from L_4 to S_2 was executed on Aug. 5, 1958. She has persistent pain in the lateral thigh and leg but has maintained relief of calf cramping, coldness, and much of the numbness.

CASE 5.—D. B., a 40-year-old white male, fell across a tool box on Jan. 13, 1958, lacerating his right forearm and injuring his back. He developed gradual burning pain in the right hand, numbness of the middle finger, redness and increased sweating of the hand. He also had gradual onset of right lateral thigh pain, stiffness of the leg muscle, and coldness and numbness of the leg and foot on the right. He was placed in traction without much relief of back pain. Examination disclosed a marked spasm of the right paravertebral muscles,

and sensitivity of the skin of the low back and right flank to touch. Knee jerks were bilaterally equal, and there was no sign of vascular disease. Stellate ganglion block was performed on the right with relief of pain and sweating, and the symptoms in the upper extremity gradually subsided. Lumbar sympathetic block was then executed on the right with relief of numbness and pain up to midthigh for 2 hours. A second lumbar block again gave relief for 2 hours. On April 26, 1958, a right lumbar sympathectomy was carried out, with removal of L_2, L_3, and L_4. There was postoperative relief of numbness, pain, and coldness up to midthigh. The patient continued to have pain and spasm in the right flank and a discogram suggested a herniated nucleus pulposus on the right L_5 level. Exploration was made with removal of a small amount of degenerated nucleus material at L_5, and spinal fusion was performed. The patient became depressed postoperatively, attempted suicide in September, 1958, but recovered sufficiently to begin work in February, 1959. Soon after beginning work, he began complaining severely of pain in the back and left leg. At last examination there was pain in the left hip and left leg down to the toe, aggravated by coughing and sneezing, but there was continued relief of pain and numbness on the right.

DISCUSSION

Case 1 illustrates the well-known aphorism that early operative treatment of a herniated nucleus pulposus is very often followed by a good result. It is of interest in this case that the subjective symptoms of coldness and numbness of the extremity (suggestive of a vasospastic syndrome) were relieved along with the pain characteristic of a herniated nucleus pulposus by operative removal of a definite protrusion through the annulus fibrosis about 3 months after acute exacerbation of difficulties. In the remaining cases, although leg pain was present preoperatively, there were leg cramps, coldness, and numbness which appeared more pronounced after discectomy. Lumbar sympathetic blocks relieved these symptoms very remarkably, and therefore lumbar sympathectomy was performed with resultant relief of the numbness, coldness, and cramps, and some of the pain, particularly in the legs.

Cases 4 and 5 had considerable relief of pain, pronounced relief of cramps, numbness, and coldness, but both continued to suffer back and thigh pain. Case 5 had symptoms in the opposite leg, suggesting nerve root compression. Such cases give rise to the question of whether bilateral lumbar sympathectomy might not be more effective than unilateral in restoring neural circulation.

The level of ganglionectomy in Cases 2 and 3 was L_1 through L_4 while in Cases 4 and 5, L_2 through L_4 only were removed. It is probable that some of the continuing difficulties in the latter 2 cases were due to inadequate sympathectomy or failure to remove accessory ganglia or pathways.

The relationship between the sympathetic nervous system and the peripheral vascular tree has been known for many years and modification of sympathetic control of these vessels has been carried out by means of chemicals and surgery. The relationship between the sympathetic and the peripheral nervous system, however, has not received much attention. The relief of numbness in these cases prompted a review of previous work on this subject since it was felt that relief of numbness must be due to an indirect effect on the peripheral nerves.

As pointed out by Adams[1] in a very comprehensive review of the anatomic and physiologic aspects of the vascularization of nerves, "all nerves except the terminal ramification receive blood vessels which traverse the epineureum to

enter the intrafascicular connective tissue (perineureum). Each nerve receives a series of vessels, each of which derive from the nearest available source, that is, a main arterial trunk alongside which a nerve is running, or, less frequently one of its muscular branches if this should pass very close to the nerve. . . . It is quite clear, therefore, that the blood supply of nerves is regional."

Adams reviews Adamkiewics' work and states "The spinal ganglia receive their blood from two sources: (1) a direct supply from the corresponding segmental artery by way of its spinal branch. In the case of the cervical ganglia where the spinal vessels arise from the vertebral artery, the latter also contribute direct branches to the ganglia. Generally, it is the radicular branch of the spinal vessels which is the primary source of supply. (2) an indirect supply, by vessels passing outward in the nerve roots (particularly the dorsal nerve roots) from the vascular channels on the surface of the spinal cord (anterior and posterior arteries)." Also "It has been conclusively demonstrated that every nerve contains a comparatively rich vascular plexus, the meshes of which are arranged longitudinally."

Studies by Bergmann and Alexander[2] have shown beadlike dilatations of the capillaries and precapillaries in spinal ganglia. The precapillary area of the peripheral vascular bed has been found by Zweifach and associates[7] to be a sphincter area motivated by muscle cells. This suggests at least a morphologic similarity between the vascular bed of the ganglia and other peripheral vascular beds.

Adams[1] further states, "It is well known that the larger branches of the nutrient arteries running in the epineureum and perineureum have a well developed tunica media composed of smooth muscle fibers; it is a just inference, therefore, that these vessels are contractile. Furthermore, nonmedulated nerve fibers (Nervi nervorum) have been demonstrated in the epineureum and perineureum. Certain of these have been shown to terminate in end bulbs and have, therefore, been regarded as sensory in function. Others, however, are intimately associated with the intraneural vessels and are probably vasomotor in function, i.e. they are postganglionic sympathetic excitor fibers supplying the arteries of the nerve."

Carli,[4] in 1950, reviewed work by Diez, Jano, and others which indicated that the paralysis in Pott's disease was in some instances aggravated by a spastic or ischemic circulatory disturbance in the vasa nervorum of the spinal cord, and that lumbar sympathectomy could cause a regression of paralysis in some cases. His own case was not relieved of paralysis by lumbar sympathectomy, but he felt that some increased nerve function was obtained. English and Spriggs[5] studied 18 cases in which findings were compatible with herniated nucleus pulposus. They subjected 7 patients to lumbar sympathetic block with complete relief of symptoms for several hours, then 11 patients were given tetraethylammonium chloride with complete relief for from 30 minutes to several days in 8, some improvement in 2, and no benefit in 1. Their suggestion was that either efferent pain-carrying fibers were affected by the drug or that a vasospastic phenomenon caused by the pressure of the herniated disc was relieved by the drug or by lumbar sympathetic block.

The above observations show that the peripheral nerves, nerve roots, and ganglia have a vascular supply which itself is anatomically similar to the vascular supply of other organs and suggest that the function of this vascular supply may be modified by the sympathetic nervous system.

The relief given in our cases by lumbar sympathectomy with respect to the numbness, coldness, and cramps, in 1 case an intermittent claudication type of cramp, is very similar to the relief afforded individuals with peripheral vascular disease in certain instances. Although most authorities believe intermittent claudication is not often benefited by sympathectomy, night cramps often are relieved. The question arises of whether some of the benefit in such individuals is due to dilation of peripheral vessels or due to sympathectomy effect on spinal cord or nerve roots and trunks which may be somewhat ischemic.

The exact physiologic action which takes place in the cord, ganglia, roots, and trunks following sympathectomy is not clear. Bulbring and Burn[3] have studied the problem with somewhat confusing results. They demonstrated in preparations in which the vascular supply to the nerves could be changed that nerve block occurred as the vascular tone became reduced. The found that ischemia need not be complete in order to produce a significant effect upon the transmission of the nerve impulse. They found it difficult, however, to explain how the impulse became restored either by the addition of vasconstrictor substances (Adrenalin and Pituitrin) to the perfused blood or by stimulation of the lumbar sympathetic chain.

That sympathectomy has a place in the treatment of patients who have had laminotomy for one reason or another and have continued to have symptoms in the leg, particularly those of numbness, coldness, and cramps and pain, seems obvious from the above considerations. Possibly some long-standing cases of sciatica, characterized by the description of "a burned out disc" might benefit more by sympathetic nerve surgery than by exploration of the interspaces and nerve roots with the subsequent scarring or operative trauma incident to exploration.

It is clear that this subject requires further study both clinically and in the experimental laboratory.

CONCLUSION

1. Five patients with symptoms of sciatic pain, numbness, coldness, and cramps are presented. One patient was relieved completely by early herniated disc removal. The other 4 patients who had been subjected to disc surgery or laminectomy and spine fusion for spondylolisthesis were relieved of their symptoms by lumbar sympathectomy.

2. It is suggested that some of the manifestations of herniated nucleus pulposus, sciatica, or postdisc syndrome are due to altered vascular supply of spinal cord, nerve roots, ganglia, or peripheral nerves.

3. Previous anatomic, physiologic, and clinical work supporting this thesis is reviewed.

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THE MECHANISM OF VAGUS INFLUENCE ON THE HORMONAL PHASE OF GASTRIC ACID SECRETION

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RECENT contributions to the understanding of the physiology of the gastric antrum have demonstrated that the vagus nerves are capable of producing the release of the hormone gastrin.[3, 4, 5] The exact mechanism by which the vagi produce this release of gastrin has not been clear. It has been assumed by several investigators that vagally induced antral peristalsis is the means by which gastrin is released.[1, 3, 5] Another possible explanation for this phenomenon is that the vagus nerves supply fibers, either directly or via the intrinsic plexuses of the antral wall, to the antral mucosa which when stimulated affect the release or secretion of gastrin. The following studies were designed to test this latter hypothesis.

METHOD

Dissection of the entire submucosal layer of the gastric antrum (antroneurolysis)[2] was performed on a series of 6 Heidenhain pouch dogs to separate the mucosa of the antrum from its extrinsic innervation. Isolated antral pouches were then constructed in these dogs, leaving vagal innervation to the antral muscular layers intact. Gastrointestinal continuity was re-established by means of a gastrojejunostomy. These antral pouches were subjected to vagal stimulation by insulin-induced hypoglycemia. At the same time, secretions were collected from the Heidenhain pouches and motility of the antral pouches was recorded. Motility was recorded by means of a small balloon in the antral pouch which was connected to a strain gauge and recorded on a direct writing recorder. Vagal stimulation was produced by giving each dog 10 units of crystalline insulin intravenously.

Isolated, innervated antral pouches were also constructed in a control group of 4 Heidenhain pouch dogs without antroneurolysis. The effect of insulin hypoglycemia on Heidenhain pouch secretion and antral pouch motility was studied in these animals.

RESULTS

Heidenhain pouch acid secretion in the control dogs with isolated innervated antral pouches was uniformly increased when these dogs were given 10 units

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of crystalline insulin intravenously. The antral motility record demonstrated an increase in antral peristalsis with the onset of hypoglycemia, signaling an increase in vagal activity (Fig. 1).

In marked contrast, the dogs with the antroneurolysed antrums showed only an increase in antral peristalsis without an accompanying secretion of acid from the Heidenhain pouch (Fig. 1).

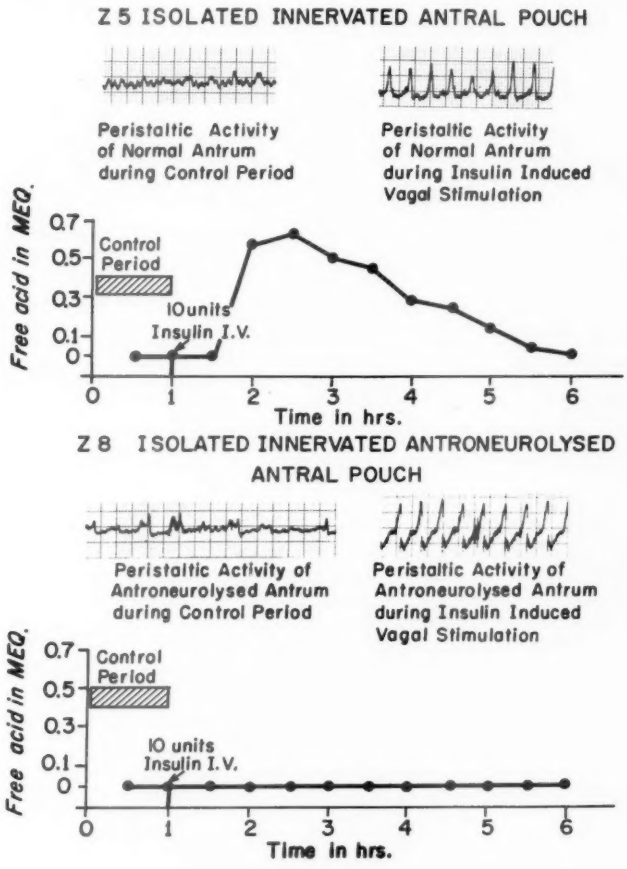

Fig. 1.

DISCUSSION

There is now ample demonstration that the vagus nerves are capable of causing the release of gastrin.[3-5] Oberhelman[3] and Woodward[5] have both shown that with the increase in antral peristalsis following vagal stimulation there is release of gastrin from the isolated innervated antral pouch. The results reported here confirm the findings of these investigators. They believe that the peristalsis of the antrum is responsible for the release of gastrin. The failure of the antrum to release gastrin after antroneurolysis indicates that antral peristalsis is not an important factor in gastrin release mechanism. These results suggest that the vagus nerves supply fibers, either directly or via the intrinsic plexuses of the antral wall, to the antral mucosa which when stimulated affect the release or secretion of gastrin.

SUMMARY

The vagus nerves are capable of releasing gastrin. It has been assumed that vagally induced peristalsis is the means by which gastrin is released. The experiments performed in this study indicate that peristalsis per se is not related to gastrin release. Under the conditions of these experiments, it appears that the vagus nerves supply fibers either directly or indirectly to the antral mucosa which, when stimulated, affect the release of gastrin.

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A LONG INTESTINAL TUBE AS AN ADJUNCT TO LAPAROTOMY IN LOCALIZING THE SITE OF OBSCURE RECURRENT MASSIVE LOWER GASTROINTESTINAL HEMORRHAGE

Report of a Case

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RECURRENT or persistent massive bleeding from the lower gastrointestinal tract occasionally arises from a lesion which is too small to be detected by inspection or palpation of the unopened intestine at operation. Such a lesion may be localized during active hemorrhage by examining the most proximal segment of intestine which contains intraluminal blood.[2] There are circumstances, however, when the level of intraluminal blood does not indicate the location of the bleeding point. Bleeding into the distal colon may fill the lumen by retrograde flow as far as the ileocecal valve or terminal ileum. Thus, the upper level of blood in the colon may be a considerable distance from the bleeding site. In the small intestine, blood is quickly propelled beyond the lesion by peristaltic activity. Therefore, unless the bleeding actively continues during laparotomy, the level of blood in the small gut may be considerably lower than the bleeding site.

The use of a long intestinal tube as an aid to laparotomy in localizing the source of obscure lower gastrointestinal bleeding has been previously suggested.[1, 3, 4] The following is a description of the successful localization of an obscure bleeding point in the colon by this method.

CASE REPORT

J. O., a 57-year-old Negro man, was admitted to the Philadelphia General Hospital on March 10, 1959, complaining of bleeding from the rectum of 12 hours' duration. This was associated with syncope.

There was a previous history of a laparotomy in 1952 for obstructive jaundice. The operative findings were interpreted to be a nonresectable carcinoma of the head of the pancreas despite a biopsy which revealed chronic pancreatitis. A palliative cholecystojejunostomy was performed. His subsequent continued improvement belied the diagnosis of carcinoma. An admission was recorded in 1956 for bright red rectal discharge. This was attributed to hemorrhoids which were excised. Preoperative gastrointestinal barium x-rays were normal. Several months later, the bleeding recurred and a second hemorrhoidectomy was performed. Radiographic examination of the gastrointestinal tract was again normal. Following discharge from the hospital, he experienced no further gross bleeding until the present episode but he exhibited a mild anemia and signs of pancreatic insufficiency.

On examination, the patient was thin and pale. The blood pressure was normal but the pulse rate was slightly elevated. There was a firm, ill-defined mass in the epigastrium. Sigmoidoscopy was normal except for the presence of red blood coming from above.

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The hemoglobin was 4.8 Gm. The blood coagulation mechanism was found to be normal. Barium x-ray examination of the intestine failed to demonstrate a lesion. However, an upper gastrointestinal series revealed slight displacement of the gastric antrum consistent with pancreatic mass. Gastric analysis revealed a moderate hyperacidity, but no blood was found in the aspirate.

An ulcer regimen was begun despite the lack of evidence of ulceration, but was finally abandoned as valueless. During the next 5 weeks in the hospital the patient bled massively from the rectum four times and also experienced many episodes of minor rectal bleeding. A total of 20 units of blood was required to replace the blood loss. Throughout this period repeated barium x-ray studies and sigmoidoscopic examinations were nonrevealing.

On April 25, 7 weeks after admission, a Miller-Abbott tube was passed into the stomach. Intermittent aspirations from the tube were blood free the next day despite the recurrence of melena. During the next 4 days as the tube traversed the small intestine, serial aspirations remained free of blood. However, on April 30, bright red blood was aspirated for the first time. Abdominal x-ray examination revealed that the tip of the tube had reached the cecum (Fig. 1). Operation was promptly performed.

Fig. 1.—Abdominal x-ray showing tip of intestinal tube in cecum.

At laparotomy, external inspection and palpation of the cecum as well as the remaining colon and small intestine were normal. Intraluminal blood could not be seen. Examination of the pancreas revealed a large mass consistent with chronic pancreatitis. Despite the absence of external evidence of disease, the anterior cecal wall was incised over the tip of the Miller-Abbott tube. Examination of the mucosa in this area revealed a small polyp with a hemorrhagic surface. The polyp was excised. Inspection of the mucosa of the remaining cecum and proximal ascending colon showed no other lesions.

The specimen measured 0.7 by 0.5 cm., and was identified as an adenomatous polyp on microscopic examination.

The patient was discharged 10 days postoperatively. There has been no further gastrointestinal bleeding.

DISCUSSION

It is unlikely that the cecal polyp would have been discovered if our attention had not been directed to the cecum by the Miller-Abbott tube. Since the patient's last hemorrhage had been a mild one, the level of intraluminal blood was not discernible, and could not be used as a guide to the lesion. If laparotomy had been performed during an episode of massive hemorrhage, it is likely that the entire colon would have been filled with blood. Discovering the bleeding point in those circumstances would have been fortuitous.

SUMMARY AND CONCLUSIONS

Utilizing the highest level of intraluminal blood as a guide to the bleeding site at laparotomy during active hemorrhage has limitations in colonic lesions and in small intestinal bleeding which has stopped just before operation. A patient is presented in whom a long intestinal tube helped to locate at laparotomy a cecal polyp which was too small to be demonstrated radiographically. We believe that the long intestinal tube may be a useful adjunct to laparotomy in selected patients with persistent or recurrent massive bleeding from the small intestine or proximal colon when the usual preoperative investigative measures fail to locate the bleeding lesion.

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PENETRATING WOUNDS OF THE DIAPHRAGM

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THE most trivial laceration of the diaphragm possesses the potential for developing into a serious and complicated surgical problem. Penetrating wounds of the diaphragm are the most frequent cause of traumatic diaphragmatic hernias.[7] It seems apparent that at times lacerations of the diaphragm are either overlooked when the patient is first seen, or the laceration is considered too minor to warrant repair. The mechanism[3] of development of a large diaphragmatic hernia from a small stab wound, particularly on the left side, is that, first, a small tag of omentum herniates through the opening. Then, with the motion of the diaphragm, combined with the lower pressure in the pleural space as compared to the higher pressure in the abdomen, more and more omentum is pulled through the opening into the chest, stretching the opening larger. Eventually the opening is large enough to admit stomach, colon, spleen, or other organs.

The purpose of this paper is to present 3 complicated cases of diaphagmatic hernia resulting from penetrating wounds. A review of the records at the University of Texas Medical Branch Hospitals reveals that in the 10-year period from 1949 to 1959, 17 patients with traumatic diaphragmatic hernias were seen. Of these, 6 were due to stab wounds of the chest which lacerated the diaphragm; one was due to a gunshot wound, and the remainder were due to blunt trauma. In the same period, 24 patients with acute penetrating wounds of the diaphragm were operated upon and the defect in the diaphragm repaired. Of these 9 were due to gunshot wounds and 15 were due to stab wounds of the chest. In a recent report[8] from this institution of 152 penetrating abdominal wounds, 20 of these wounds had entered the peritoneal cavity through the chest and diaphragm.

CASE REPORTS

Three complicated cases of diaphragmatic hernia due to stab wound have been selected for presentation, since they demonstrate clearly the sequence of events which can follow overlooked lacerations of the diaphragm at the time of trauma, particularly of penetrating trauma.

CASE 1.—A 22-year-old Latin-American man was admitted to the University of Texas Medical Branch Hospitals on June 20, 1958. History revealed that 6 days prior to admittance to the hospital he developed cramping, epigastric pain, nausea, vomiting, and obstipation. These symptoms were progressive in nature. Past history revealed that 4 years previously, the patient had received multiple stab wounds of the abdomen and left chest. A liver laceration was repaired at laparotomy.

Examination showed the abdomen to be distended and tympanitic, and occasional peristaltic rushes could be heard. There was a stab wound scar in the left sixth intercostal space at the mid-axillary line. There was also a small stab wound scar in the midline

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on the back at the level of T_{10}, and to other wounds on the right posterior chest at the level of the eleventh and twelfth ribs. There were also several scars on the abdomen.

Flat and upright scout films of the abdomen showed marked distention of the transverse colon. The chest film revealed a loop of gas-filled bowel above the left hemidiaphragm (Fig. 1).

Immediate exploratory laparotomy was performed and the splenic flexure of the colon was found to be incarcerated through a 4.0 cm. rent in the diaphragm. The thick fibrous ring was opened and the colon and omentum reduced into the abdomen. The defect in the diaphragm was repaired and the abdomen closed in layers.

The postoperative course was uneventful.

CASE 2.—A 29-year-old Latin-American man was admitted to the University of Texas Medical Branch Hospitals on Sept. 19, 1958, after having been admitted to another hospital 10 days previously with cramping epigastric pain. He had continued, however, to eat and pass bowel movements up to 2 days prior to admittance here. Seven days prior to admittance here, however, a chest x-ray revealed pleural fluid on the left. Repeated thoracentesis had yielded up to 1,850 c.c. of fluid from the left chest. On Sept. 15, 1958, 4 days prior to admittance to John Sealy Hospital, a mushroom catheter was placed in the chest and more fluid removed. On Sept. 19, 1958, feces were noted to be draining from the catheter and then the patient was referred to this hospital.

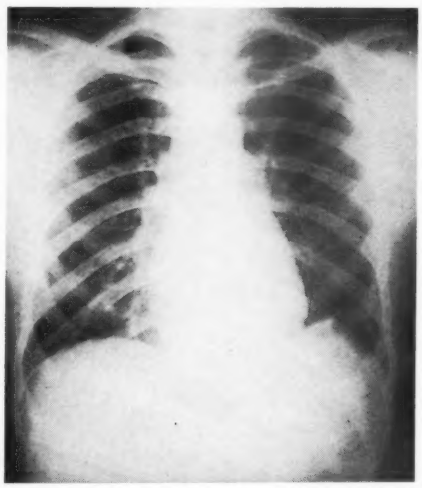

Fig. 1.

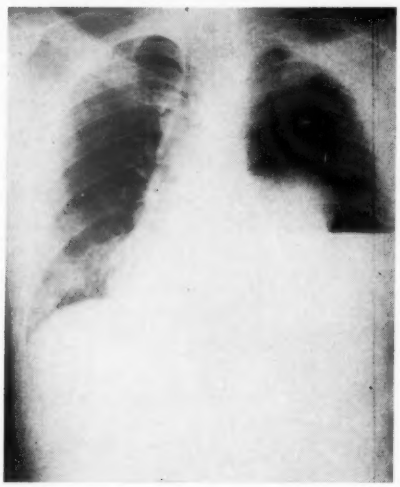

Fig. 2.

Fig. 1.—Case 1. Posteroanterior chest film revealed a loop of gas-filled bowel above the left hemidiaphragm.

Fig. 2.—Case 2. Posteroanterior chest film revealed left hydropneumothorax with complete atelectasis of the left lung.

Past history revealed that this patient had been stabbed in the left anterior chest in 1954. Chest x-ray on admittance Sept. 19, 1958, revealed a hydropneumothorax on the left with complete atelectasis of the left lung (Fig. 2). It was postulated that the patient had a traumatic diaphragmatic hernia resulting from the old chest wound, and that the colon had become strangulated in the hernia, resulting in the pleural fluid in the beginning. As the loop necrosed, the pleural fecal fistula developed.

A diversionary transverse colostomy was done on Sept. 19, 1958. Following this the chest was placed on suction and irrigated frequently with normal saline and 0.5 per cent neomycin solution. On Oct. 2, 1958, left thoracotomy was performed. The segment of colon in the left chest was resected and an end-to-end anastomosis done. The colon was returned to the abdomen and the diaphragm repaired. A decortication of the left lung was also carried out. The procedure was accompanied by brisk bleeding, requiring multiple transfusions for replacement of blood loss.

The postoperative course was very stormy. Several days postoperatively, he developed marked icterus which was thought to be due to hemolysis following transfusions. On Oct. 8, 1958, he developed massive upper gastrointestinal hemorrhage which required an additional 7,000 c.c. of blood. Because the bleeding could not be controlled by nonoperative methods, emergency laparotomy was performed on Oct. 8, 1958, and a large bleeding duodenal ulcer was found. It was thought that this ulcer was most likely a "stress ulcer." Gastric resection was done. The patient tolerated the procedure poorly, became anuric, and died 24 hours later.

CASE 3.—A 48-year-old Negro woman was referred to the University of Texas Medical Branch Hospitals with a provisional diagnosis of a large lipoma of the posterior chest wall (Fig. 3). The patient stated that 8 years previously she had sustained a laceration in this area. About 1 year after the injury, a swelling in the area was noted. This gradually increased in size. She noted that the mass would get tight when she coughed, and it seemed to have bowel "growling" in it at times.

Fig. 3.

Fig. 4.

Fig. 3.—Case 3. Large diaphragmatic hernia resulting from stab wound between tenth and eleventh ribs in mid-axillary line.

Fig. 4.—Case 3. Lateral chest film revealed gas-filled bowel between tenth and eleventh ribs in mid-axillary line.

Examination revealed a 10 by 10 cm. soft tissue mass on the left posterolateral chest wall which became more prominent with straining. Bowel sounds were audible over the mass. A healed scar of the repaired laceration was present over the mass.

Chest film in the lateral projection revealed gas-filled bowel within the mass (Fig. 4). Barium enema confirmed the presence of the splenic flexure of the colon external to the rib cage (Fig. 5).

On Oct. 19, 1958, the patient was operated upon and it was found that the splenic flexure of the colon and the omentum had herniated through the diaphragm and then between the tenth and eleventh ribs in the mid-axillary line. The bowel was reduced into the abdomen and the defect in the diaphragm and chest wall repaired. The patient made an uneventful recovery, except for a minimal wound infection which cleared with proper drainage.

DISCUSSION

The urgency of immediate laparotomy in stab wounds of the abdomen is well recognized.[5, 6] When the stab wound is above the costal arch, however, there is a tendency to be lulled into a feeling of false security, since the possibility of combined thoracoabdominal injury is overlooked. Likewise, gunshot wounds penetrating the region of the diaphragm are less likely to be overlooked than are stab wounds. Stab wounds in the region of the diaphragm require immediate exploration for at least two reasons: (1) for repair of possible injury to abdominal viscera and (2) for repair of the laceration of the diaphragm to prevent the later development of a diaphragmatic hernia.

In the 3 cases presented above, serious difficulty, and in 1 case death, may have been prevented by immediate repair of the diaphragmatic defect at the time of injury. In Case 1 a laparotomy had been done for the injury to the liver, but the diaphragmatic injury had been left unrepaired.

The literature[1-3, 7] contains many cases of similar injuries in which nothing has been done at the time of injury, but difficulty has developed months or years later when herniation occurred.

Fig. 5.—Case 3. Barium enema confirmed the presence of the splenic flexure of the colon external to the rib cage.

The diagram (Fig. 6) shows how the diaphragm is in apposition with the chest wall from the lower rib margin up to the level of the seventh rib in the mid-axillary line. In this area, the thoracic cage and diaphragm serve as a continuation of the abdominal wall, overlying abdominal viscera rather than lungs. Exploratory laparotomy for stab wounds in this region is as mandatory as laparotomy for stab wounds below the costal margin. The danger of injury to intra-abdominal organs is considerable. In each of the 24 penetrating

wounds in this series treated by emergency laparotomy, there was damage to intra-abdominal organs. Even though no viscera are injured, there still may be a laceration of the diaphragm which should be repaired.

As demonstrated in Fig. 6 the diaphragm is still near the chest wall as it curves to the dome, which, in maximum expiration, is about the level of the fourth costal cartilage anteriorly. Exploration is probably required in most of the instances of penetrating injury in this area. Of course, judgment should be used, and consideration should be given to the type of weapon, its length, and so forth. Exploration here need not necessarily be immediate, especially in patients with other severe injuries, and whose general condition would make exploration hazardous. In those borderline cases with wounds about the level of the fourth or fifth ribs, one may elect to follow at intervals with chest x-rays to watch for the development of a hernia at a later date. Exploration of wounds on the right side above the level of the seventh rib in the mid-axillary line is usually not necessary because the liver prevents abdominal contents from herniating through the diaphragm.

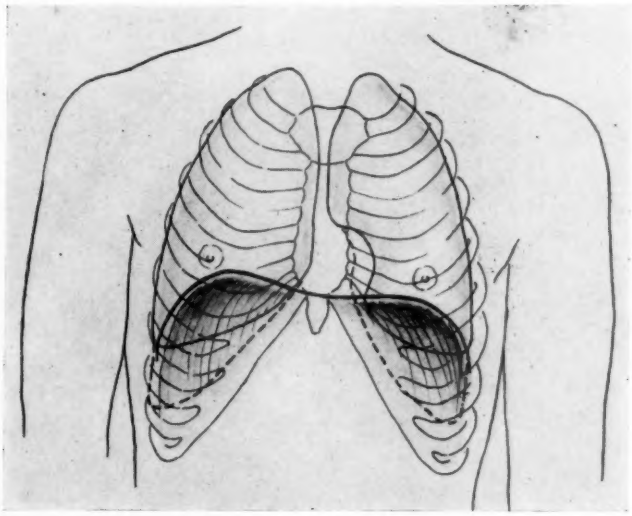

Fig. 6.—The diagram shows the relationship of the diaphragm to the chest wall, particularly in the mid-axillary line. The diaphragm is in apposition with the chest wall from the lower rib margin up to the level of the seventh rib.

The choice of laparotomy or thoracotomy for repair of diaphragmatic injuries will depend to some extent on the individual surgeon's field of major interest. It is certain that all areas of the left diaphragm can be approached from the abdominal side. Also, the abdominal viscera may be explored with greater ease from the abdominal side. It is felt that most acute stab wounds of the diaphragm should be approached through the abdomen. Harrington[4] recommends the transabdominal approach for repair of all traumatic hernias of the left hemidiaphragm. Others feel that these hernias can be repaired more securely through the thoracic approach.

The late complications in the 3 cases presented here point up the fact that lacerations of the diaphragm should be repaired immediately if at all

possible. Also, once a traumatic diaphragmatic hernia develops, it should be repaired whether it is symptomatic or not.

SUMMARY AND CONCLUSIONS

1. Three cases demonstrating late complications of stab wounds of the diaphragm are presented.

2. Stab wounds of the chest below the level of the seventh rib in the mid-axillary line demand laparotomy in most instances.

3. The defect in the diaphragm, regardless of its size, requires repair.

4. All traumatic diaphragmatic hernias should be repaired when diagnosed, whether symptomatic or not, if the general condition of the patient permits.

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SILENT THROMBOSIS IN MAJOR LIMB ARTERIES—A POSTOPERATIVE HAZARD

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SURGEONS and physicians are well aware of the complication of venous thrombosis which may arise following surgery or any acute medical illness. That arterial thrombosis, often of a silent nature, can occur as a postoperative complication with surprising frequency is possibly not so well known or appreciated.

This fact became apparent when the mode of onset of intermittent claudication in a group of patients with peripheral vascular disease was reviewed. In one group, the onset was gradual and unrelated to previous illness or operation. In another, the onset followed an attack of severe pain in the calf muscles consistent with an incidence of acute arterial thrombosis. In yet a third group, however, the symptoms of intermittent claudication first appeared following surgery. In 2 patients it developed after an acute medical illness. None of these patients experienced pain in the legs while they remained in the hospital, and only after returning home and increasing their activity and walking distance did they become aware of cramping pain in the leg.

The brief history of 6 such patients illustrates the sequence of events.

CASE REPORTS

CASE 1.—Mrs. C., a 52-year-old woman, was a keen golfer and played regularly. She was operated upon for gallstones and a cholecystectomy was performed. The day following operation she became seriously ill and remembers little of the next 2 days except that she was seen by many doctors. What actually happened at this time cannot be ascertained from the records of the hospital where she was treated. She eventually recovered and was discharged 4 weeks after operation. During her stay in the hospital she recalls no symptoms of pain or numbness or coldness of the left leg. With increased activity over the ensuing weeks, she noticed mild cramps in the left calf after walking 2 blocks. This was relieved by rest. She reported to her doctor who reassured her that the pain resulted from "tiredness" of the calf muscles as a result of the period of confinement in bed following operation.

When seen in consultation 3 months later because of persisting symptoms in the left leg, she had typical intermittent claudication in the calf, a good femoral pulse, but no palpable pulses distally. Arteriography revealed a block of the superficial femoral artery in the adductor canal.

CASE 2.—Mr. M., a 55-year-old man, had no symptoms referable to the right leg prior to operation for partial gastrectomy. The operation and the postoperative convalescence were unremarkable except for one incident on the third postoperative day following removal of the duodenal tube when he became nauseated and felt faint. The tube was replaced and 1,000 c.c. of fluid removed.

Following discharge—similar to the patient in Case 1—he noticed pain in the right calf upon walking. When he consulted his surgeon he was told that the pain was due to muscle fatigue and as he got back his strength the pain would gradually disappear. The pain,

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however, got worse and 4 months after operation the patient had all the symptoms of intermittent claudication with absence of all palpable pulses below the common femoral artery. Arteriography revealed a complete block of the superficial femoral artery below the origin of the profunda femoris.

CASE 3.—Mr. D., a 52-year-old patient, also had a partial gastrectomy and the subsequent course and findings were exactly the same as in the patient in Case 2 except that he had no gastric retention on the third day. On the fifth postoperative night he thought his right leg felt rather cold. He was given an electric blanket by his nurse and was so much better the following day that he did not think it fit to mention the incident to his doctor!

Investigation for subsequent persistent intermittent claudication also revealed a complete block of the superficial femoral artery in the right leg.

CASE 4.—Mr. P., a 63-year-old man, was seen because of intermittent claudication of the left calf, and gangrene of the skin of the dorsum of the left foot. Six months previously he was admitted to the hospital with acute coronary thrombosis. At the time of admittance, blood pressure was 100/60 mm. Hg. Normal blood pressure was 140/80. He responded well to medical therapy and returned home in one month. At no time during his illness did he experience any pain or other symptoms in the left leg. Three months after the myocardial infarction and simultaneously with increased walking activity he noticed pain in the left calf. This progressed with the development of gangrene of the dorsum of the left foot. Arteriography confirmed the clinical findings of a complete block of the left superficial femoral artery.

CASE 5.—Mr. G., a 68-year-old man, had an abdominoperineal resection for carcinoma of the rectum 3 months prior to vascular consultation at which time he had typical intermittent claudication of the right leg. He had led an active life prior to operation with no symptoms in the leg and strenuously denied any pain or coldness of the limb during his stay in the hospital. Only with a return to active walking was claudication first noted. Operation and postoperative convalescence had been uneventful and blood pressure recordings at operation and for 48 hours postoperatively showed no significant detectable period of hypotension. Arteriography revealed a blockage of the superficial femoral artery in the adductor canal.

CASE 6.—Mr. R., a 55-year-old war veteran, developed scarlet fever and was in bed in the hospital for 4 weeks. His progress was uneventful on routine medical therapy. Upon discharge, and with increased walking activity, he developed cramps in the right leg. This persisted and when seen in consultation he had typical intermittent claudication. Subsequent investigation including aortography revealed a block of the right common iliac artery. At no time during his stay in the hospital did he notice any pain in the right leg whatsoever. Prior to his medical illness he was accustomed to going on 10 mile route marches without difficulty. On close questioning he stated that he thought the right leg had felt slightly colder than the left for some months prior to admittance to the hospital.

DISCUSSION

Acute arterial thrombosis with symptoms, occurring as an isolated event or following surgical operation or medical illness, is well recognized. Postoperative coronary thrombosis or cerebral thrombosis is by no means rare.

It would appear that severe occlusion, especially of the lower limb arteries, can occur silently and without immediate symptoms, much more commonly than is usually suspected. It would be a bold, and probably unwise, clinician who would deny any connection between the overt symptoms of arterial insufficiency which developed in the 6 patients reported and the events which preceded them—operation in 4 cases and an acute medical illness in 2 others.

Unfortunately, there is no record of these patients' peripheral pulses prior to operation. Some of them may have been absent or diminished at that time. Be that as it may, they all subsequently developed a sufficiently severe degree of arterial blockage to give rise to intermittent claudication and, in one case, gangrene. From the appearance of the arteriograms it would seem highly probable that all 6 patients had pre-existing arterial disease and that the subsequent symptoms developed from an extension of this process. Some may have had incomplete occlusion of the artery progressing to complete blockage. Others may have had an area of localized complete occlusion with subsequent proximal or distal extension.

PREVENTION AND TREATMENT

The sequence of events in the reported cases would seem to be as is shown in Fig. 1.

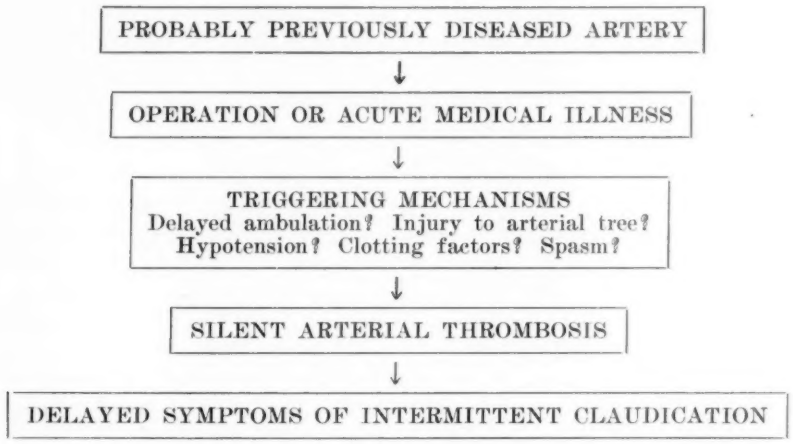
PROBABLY PREVIOUSLY DISEASED ARTERY
OPERATION OR ACUTE MEDICAL ILLNESS
TRIGGERING MECHANISMS
Delayed ambulation? Injury to arterial tree?
Hypotension? Clotting factors? Spasm?
SILENT ARTERIAL THROMBOSIS
DELAYED SYMPTOMS OF INTERMITTENT CLAUDICATION

Fig. 1.

As with many other postoperative complications the treatment of silent arterial thrombosis must be directed toward its prevention. In regard to this the following factors would seem worthy of consideration.

Awareness of the Problem.—If the hazard of silent arterial thrombosis be remembered, a careful history of possible arterial insufficiency of the limbs should be noted, together with careful examination and recording of limb pulses, temperature changes in the legs and possible oscillometric readings. The absence of any major pulse in the limbs should alert the surgeon to the possibility of subsequent arterial thrombosis.

Early Ambulation.—Early ambulation is probably of major importance. We are all very conscious of the dangers of venous thrombosis and pulmonary embolus. When operating upon married women, a most careful inquiry about possible phlebitis in previous pregnancies is made and, if there is any such history, we are particularly vigilant regarding early ambulation following surgery. Similarly—and especially in male patients—any history or clinical findings suggestive of arterial disease should make us even more insistent on early postoperative ambulation and movement of the lower limbs.

Protection of Arterial Tree During and After Operation.—Just as anesthetists are very conscious of brachial plexus injuries while positioning patients on the operating table, surgeons should be careful to avoid pressure on major arteries to the limb during operation. The use of acutely angled metal knee cradles when operating with the patient in the lithotomy position, the unnecessary use of tourniquets, or weary assistants leaning on the patients limbs and compressing the femoral arteries are all details to guard against during operation. Tight bandaging of the legs without adequate padding must also be avoided.

Prevention of Hypotension During and After Operation.—Prevention of hypotension is desirable for so many other reasons that it really needs little emphasis. It is especially important to avoid it during the actual operation. The possibility of silent arterial thrombosis is but another hazard to add to the many which may supervene should a significant drop in blood pressure develop during or immediately following surgery. It may also give added pause to anesthetist and surgeon alike before contemplating the use of hypotensive drugs or spinal anesthesia in certain patients and it should certainly convince them of the vital necessity of adequate preoperative restoration of blood volume when operating upon chronically ill, elderly patients whether they be male or female.

The incautious use of postoperative sedatives is another source of possible hypotension. An efficiently well-staffed recovery room where frequent blood pressure recordings are taken must surely play an important part in avoiding arterial thrombosis in the immediate postoperative period.

Other measures to avoid hypotension really comprise all the many facets of good surgical care both at operation and afterward.

Anticoagulants.—It would seem reasonable to consider postoperative anticoagulant therapy if, for any reason, we are led to suspect that any patient faces the possible hazard of arterial thrombosis in greater degree than the normal patient. Such a patient may show clinical evidence of impaired arterial supply to the legs prior to operation.

Furthermore, the findings of Heimbecker and Bigelow,[1] and Zenderfeldt,[3] as well as my own,[2] would seem to indicate that vascular stasis with agglutination of erythrocytes is greatly enhanced following disease and trauma—be it operative or otherwise.

Prevention of Arterial Spasm.—It is difficult to say whether arterial spasm may or may not play an important part in the development of silent arterial thrombosis, but there is probably little we can do about it. The use of prolonged vasoconstrictor drugs should certainly be avoided where possible but as the complication of hypotension often dictates their use, and as the latter complication is most to be feared, inevitably situations will arise where a proper evaluation has to be made as to what is best for the patient. If hypotension can be corrected by other means such as the replacement of blood volume, then obviously this should be done.

Prevention of Silent Arterial Thrombosis Following Acute Medical Illness.—Apart from the preventive measures which concern the surgeon and

anesthetist preoperatively and during operation, those preventive measures already outlined would seem to apply equally well to the physician as they do to his or her surgical colleagues.

Sex Factor.—Since peripheral vascular disease is so much more common in the male, it is obvious that men face a greater hazard than women in developing silent arterial thrombosis following operation.

Treatment of the Established Case.—Once arterial thrombosis has developed, the treatment must follow that of established, present-day practice and will naturally include a consideration of arterial grafting should the symptoms warrant it and the results of arteriography give good prospect of success.

A WORD OF CAUTION

It is obvious, of course, that the benefit of a necessary surgical operation must not be denied the patient who has evidence of associated arterial disease but, if we are aware of the fact that such a patient runs additional risks, then perhaps we can at least minimize or circumvent them in certain cases.

SUMMARY

Six cases of silent arterial thrombosis, 4 following operation, are reported. Two followed acute medical illnesses.

All 6 patients developed persistent intermittent claudication when they began to walk.

The possible mechanisms which may be involved in the development of this type of thrombosis and the preventive measures which it would seem reasonable to implement are outlined.

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ARTERIAL EMBOLISM WITH ACUTE MASSIVE ISCHEMIC MYOPATHY AND MYOGLOBINURIA

Evaluation of a Hitherto Unreported Syndrome With Report of Two Cases

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THE purpose of this paper is to present a hitherto unreported syndrome consisting of arterial embolism of the extremities associated with acute massive ischemic myopathy and myoglobinuria. The clinical pathologic picture herein described is based on 2 cases. In each instance, the arterial occlusion resulted in sudden severe ischemia of the entire extremity with marked stiffness of the joints, associated with widespread skeletal muscle lesions and myohemoglobinuria.

CASE REPORTS

Case 1.—H. A. Hospital No. 104912. A 64-year-old white man entered Montefiore Hospital on March 27, 1959, because of rectal bleeding of about 2 weeks' duration. Sigmoidoscopy revealed a rectal polyp which, on histologic section, was found to be an adenocarcinoma. On April 6, 1959, under general anesthesia, a "pull-through" resection of the rectum was performed by Dr. G. Gerst. This consisted of resection of the rectum followed by reanastomosis of the 2 ends, with preservation of the anal sphincters. Two abdominal incisions were made: (1) a left vertical paramedian for the "pull-through" procedure, and (2) a right pararectus for the transverse colostomy. During this operation, which lasted 2 hours, the patient received 1 unit of blood.

One hour postoperatively the patient complained of severe pain in the right lower extremity. Shortly thereafter, physical examination revealed: (a) coldness of this entire extremity; (b) pronounced waxy pallor of the foot and leg and cyanotic mottling of the thigh; (c) anesthesia to pinprick up to the groin; (d) complete absence of motion of the toes, ankle, and knee; (e) marked stiffness of all these joints; (f) absence of all pulses, including that of the external iliac; (g) presence of all pulses in the left lower and both upper extremities; (h) blood pressure of 120/80 mm. Hg; (i) lack of evidence of any cardiac lesion.

The diagnosis of acute occlusion, possibly embolic, of the right common iliac artery was made. In view of the severity of the clinical findings it was felt that the distal arterial tree was probably also extensively obliterated.

Upon operation, the right common iliac artery appeared to be slightly dilated and pulseless. A whitish red, firm thrombus was easily extruded together with some atheromatous material from this artery. Except for a small area, its intima appeared devoid of atheromatous plaques. After closure of the arteriotomy, a good pulsation was felt in the common and external iliac arteries, but not in the hypogastric and femoral. The common, superficial, and deep femoral arteries were all occluded. Through an arteriotomy in the common femoral, more thrombi were removed. Since no back flow was obtained, retrograde flushing was carried out through arteriotomies in the superficial femoral in Hunter's canal and the posterior tibial arteries. After closing the last 3 arteriotomies, a pulsation was felt in the femoral, popliteal, and posterior tibial. At the completion of the procedure, the temperature and

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color of the entire lower extremity appeared to have improved. It is noteworthy that the stiffness of the toes, ankle, and knee persisted despite the anesthesia. During this procedure the patient received 4 units of whole blood.

The next morning the thigh and leg were warm, while the foot remained cool and pale. In the afternoon, the right lower extremity became massively swollen from the toes to the hip. The edema was extremely hard and nonpitting. The presence of this massive edema led to the diagnosis of superimposed venous occlusion. The foot was cold and mottled although the femoral pulse could easily be felt through the dressing.

In the first 12 hours following operation, the patient's urinary output consisted of 240 c.c. of cherry red urine. Shortly thereafter the urinary output ranged from 30 to 60 c.c. per 24 hours. At first, this was attributed to a transfusion reaction and the color of the urine to hemoglobinuria. There was, however, never an elevated plasma hemoglobin, or any evidence of jaundice. Electrophoresis subsequently demonstrated the pigment to be metmyoglobin.

The patient's anuria was treated with restricted high carbohydrate fluids containing electrolytes and calcium as indicated by daily serum chemistry studies (Table I).

TABLE I. LABORATORY FINDINGS IN CASE 1

		POSTOPERATIVE DAY											
		1	2	3	4	5	6	7	8	9	10	11	12
Date	3/27	4/7	4/8	4/9	4/10	4/11	4/12	4/13	4/14	4/15	4/16	4/17	4/18
Hematocrit value (%)	43	50	55.5	54	47	45	44	44.5	37	38	–	–	40
Blood urea nitrogen (mg./100 c.c.)	12.5	19.5	40.5	71.0	93.5	106.0	101.0	190.5		238.5	255.0	280.5	247.0
Serum Na level	–	132	127	126	129	130	133	132		138	141	141	139
Serum K level	–	5.7	8.0	6.6	6.2	6.9	7.3	7.3		5.2	4.5	4.6	6.2
CO_2 combining power	–	21.8	19.9	17.6	19.1	20.0	19.2	14.6		17.0	18.5	19.3	–
Serum chloride level	=	88.8	85.7	80.6	83.2	83.3	82.8	84.6		85.1	84.7	82.5	–
Serum Ca level	–	–	–	–	7.2	–	–	–	–	7.0	7.0	6.8	–
Serum pH level	–				8.4	–	–	–	–	8.5	9.1	10.4	–

On the third postoperative day, early gangrene of the right foot and leg up to the knee became apparent, with the femoral pulse still being felt. Edema of the right thigh had subsided considerably.

The renal shutdown was complete and the blood urea nitrogen kept rising steadily. On the fifth day of anuria, because of serum potassium of 7.3 mEq. per liter, increased duration of the QRS complex, and peaking of the T waves, he was started on sodium exchange resins. Over the next 4 days the potassium was brought down to 4.5 mEq. per liter. The following day, the right foot and leg were packed in ice and a tourniquet was applied just below the knee in order to eliminate any toxemia from the gangrenous leg. One of the abdominal wounds appeared infected, and was treated by drainage and daily irrigation.

On April 13, starch gel electrophoresis again identified the urinary pigment as myoglobin: (1) there was a benzidine positive band with characteristic mobility of myoglobin in the urine, and (2) serum haptoglobin bands were those of type 2-1 or 2-2 and were not saturated by 120 mg. per 100 c.c. of hemoglobin. This was considered to indicate that significant hemolysis had not occurred in the recent past.

Despite rigorous control of the blood electrolytes, the anuria continued unabated. On the tenth postoperative day the blood urea nitrogen rose to 280 mg. per 100 c.c. His general condition was deteriorating, his blood pressure started to fall, and reached the level of

60/40 mm. Hg on the twelfth postoperative day. In addition, he became semistuporous and exhibited generalized twitching. It was felt that extracorporeal dialysis should be attempted, although it was not expected to reverse effectively the advanced renal changes. After the artificial kidney had been used for 2 hours, he suddenly became cyanotic following aspiration of gastric contents. Although these were promptly sucked out from the respiratory tract, he developed ventricular fibrillation and died.

In postmortem, the right leg and foot did not seem to exhibit definite areas of breakdown of the skin. The ice packing of the leg accounted for this appearance. There was no evidence of intracardiac thrombosis of any recent or healed myocardial infarct. The aorta displayed several areas of atheromatous plaques, some of which were ulcerated and had a superimposed thrombus. The right iliac, common, and superficial femoral arteries down to Hunter's canal were patent. At this latter level, the lumen, of the superficial femoral artery contained a fresh thrombus, the recent nature of which was also corroborated by histologic section. The posterior tibial artery appeared patent. The 4 arteriotomy sites were all well healed. Dissection of the inferior vena cava, the iliac, femoral, and tibial veins failed to reveal any thrombotic occlusion. The gastrocnemius appeared soft and necrotic while the quadriceps femoris had a normal appearance. Histologic examination of the kidney revealed typical tubular necrosis. Microscopic study of the quadriceps femoris and the gastrocnemius showed foci of loss of striation and of sarcolemmal nuclei of muscular fibers. There was no evidence of regeneration. Several muscular vessels exhibited fresh thrombi within their lumina.

Comment: The presence of ulcerated atheromatous plaques with a superimposed old thrombus in the aorta, in the absence of any cardiac lesion, appears to be the source of the embolus. In addition, the whitish red, firm thrombus extruded from the common iliac, and the patency of the arterial tree achieved by operation seemed to lend further support to the diagnosis of arterial embolism.

CASE 2.—G. J., Hospital No. 107733. A 35-year-old Negro man was admitted to Montefiore Hospital on July 13, 1959, because of sudden severe pain in the left lower extremity of about 5 hours' duration. He was known to have rheumatic heart disease, mitral stenosis, and auricular fibrillation.

The site of pain at onset was in the left hip and gluteal region. It occurred suddenly while he was changing a tire on his car. The pain became progressively, but rapidly, more severe and radiated to the thigh. Numbness appeared shortly thereafter and involved the foot and leg up to the knee. The patient consulted Dr. J. J. Silverman who, in addition to confirming this history, had noted that the patient had been walking and strenuously exercising his left leg in an apparent attempt to overcome the pain and numbness.

Physical examination revealed coldness and anesthesia of the foot and leg, with a sharp line of skin temperature demarcation above the knee. Motion of toes, ankle, and knee was completely abolished. All the pulses of the left lower extremity, including the external iliac, were absent while all the other peripheral pulses were easily felt. Unusual findings noted were twitchings of the left thigh muscles in the groin and of both pectoral muscles. The twitching of the left psoas was almost mistaken for a femoral pulse by one observer.

Examination of all systems other than that of the heart was essentially negative. An electrocardiogram revealed auricular fibrillation. The hematocrit was 38 per cent, the white blood cell count was 5,100, polymorphonuclear cells 48, stabcells 38, eosinophils, lymphocytes 38, monocytes 1.

The diagnosis of left iliac arterial embolism was made and the patient was operated upon about 8 hours after its clinical onset. The common and external iliac arteries down to Poupart's ligament appeared occluded. Through an arteriotomy in the external iliac, just distal to the bifurcation, an embolus and a long secondary thrombus were extruded quite easily. This was followed by good retrograde flow. At the completion of the procedure the femoral pulse was bounding. About 2 hours postoperatively, a temperature level was present at midcalf and faint dorsalis pedis and posterior tibial pulses were felt. During the night, a few hours after the embolectomy, the urine appeared to be dark red, wine colored.

The next morning, July 14, 1959, about 10 hours following operation, the pedal pulses were felt, although still faintly. Eight hours later the patient complained of a sensation of heaviness in the thigh. Physical examination revealed enlargement of the thigh, knee, and upper third of the leg. A definite temperature level was present at midcalf and a blotchy discoloration had appeared on the lateral aspect of the leg. Anesthesia up to the knee was present and motion of toes, ankle, and knee was again abolished. The popliteal and pedal pulses were no longer palpable. It was felt that a new arterial occlusion had occurred together with an iliofemoral vein obstruction. With the patient under spinal anesthesia, exploration of the iliac and femoral vessels was performed which showed the arteries to be pulsating normally and the iliofemoral veins to be patent. Exploration of the popliteal vessels revealed the veins to be patent, while the artery appeared spastic and pulseless. Through an arteriotomy, however, pulsatile blood was obtained from the proximal end although backflow was less pronounced. No evidence of thrombus was found after several attempts at catheterization of the femoral artery.

Unusual findings uncovered during this exploration of the iliac, femoral, and popliteal vessels concerned the appearance of the various muscles. The psoas, sartorious, biceps, and gastrocnemius appeared edematous and pale, but with no evidence of edema in the subcutaneous tissue.

The urine continued to be colored red, with a benzidine positive pigment, which upon paper electrophoresis was identified as myoglobin. The serum showed normal haptoglobin pattern (type 2-2) upon starch gel electrophoresis. The hemoglobin-binding capacity was 350 mg. per cent (normal values being about 120 mg. per cent). The normal level of haptoglobin in the serum ruled out the possibility of hemoglobinuria and was an additional confirmation that the urinary pigment was myoglobin. Other laboratory findings failed to disclose serious renal changes (Table II).

TABLE II. LABORATORY FINDINGS IN CASE 2

	DATE				
	7/13	7/14	7/16	7/21	7/27
Hematocrit value (%)	41	42.5	–	39.5	–
Blood urea nitrogen (mg./100 c.c.)	14	–	20.5	–	25.0
Serum Na level	–	133	–	134	–
Serum K level	–	5.9	–	5.1	–
CO_2 combining power	–	17.4	–	23.5	–
Serum chloride level	–	93.2	–	93.1	–

On July 15, 1959, the edema of the thigh and leg having increased, a fasciotomy in Hunter's canal was performed in the hope of freeing the femoral vessels from external pressure. The superficial femoral artery was found to pulsate down to the adductor magnus foramen. At this point, through an arteriotomy, thrombi were extruded by massaging the popliteal artery. Shortly after closure of the arteriotomy, the thrombus was reformed and it appeared futile, after the second thrombectomy, to pursue this procedure.

Again it was noted that the vastus medialis, the sartorius, and the hamstring muscles were edematous and pale. After incision of the aponeurosis, bulging of the muscle mass was most striking. This procedure did not alter the course of the ischemic manifestations. Massive edema of the thigh and leg persisted for another 5 days and then started to subside. In the meantime, gangrene of the foot and leg became apparent.

On July 23, 10 days after the onset of the acute arterial occlusion, a midthigh amputation was performed. Healing of the stump took place within 2 weeks.

At the level of the amputation the subcutaneous tissue and especially the muscles were edematous and exuded moderate amounts of clear fluid. The popliteal artery appeared

occluded by a freshly organized thrombus while the accompanying vein was patent. None of the muscular veins were thrombosed.

During the amputation, performed 10 days after the clinical onset of the embolism, 4 muscle segments were taken from the lower third of the thigh for microscopic studies. The specimens were from the rectus femoris, vastus medialis, biceps femoris, and sartorius. Gross section of these specimens disclosed some zones of hemorrhagic discoloration and some pallid-appearing areas.

Microscopic examination showed focal necrosis and regenerative changes in all 4 specimens. In some areas the muscle fibers appeared well preserved, while in some others there was loss of eosinophilic staining properties of the muscle fibers, and shrinkage and loss of normal fibrillary structures. Proliferation of sarcolemmal nuclei peripheral to the degenerate muscle tissue was present. These sarcolemmal nuclei were swollen, rounded or ovoid in shape, and had nucleoli and clumped chromatin (Figs. 1 and 2). Further evidence of degeneration within the muscle fibers consisted of occasional vacuoles. Areas of hemorrhage, scattered foci of macrophages, plasma cells, and a few polymorphonuclear leukocytes were seen.

Within some areas where the muscle fibers had completely disappeared a collection of sarcolemmal nuclei and macrophages were left filling the space previously occupied by the muscle fibers. The zones of change were fairly well demarcated but outlying fibers within the normal skeletal muscle were also subject to this change.

In conclusion, these findings appeared to represent regeneration following ischemic necrosis, the necrotic fibers being surrounded by the proliferating regenerated sarcolemmal cells.

COMMENT

Clinical Findings.—These 2 cases of acute arterial embolism are of unusual interest because of the severity of the clinical manifestations associated with ischemic myopathy and myoglobinuria.

Clinically, 4 outstanding manifestations lend to these cases their characteristics: (1) severity of the pain; (2) pronounced ischemia of tissues; (3) rigidity of the limb, and (4) massive edema.

In both cases, the patients complained of excruciating pain shortly after the clinical onset of the occlusive arterial syndrome. Any attempt at mobilizing or examining the extremity resulted in its exacerbation. The pain, although diminshed, persisted even in the postoperative period for several days. It is likely that the severity and persistance of pain were largely related to the ischemic myopathy.

The coldness, anesthesia to pinprick, waxy pallor, and cyanotic mottling, involving the entire extremity from the toes to the groin, reflected the profound degree of the ischemia. Usually in an acute occlusion of the common iliac artery the above findings do not exceed the level of the knee. It is likely that in the present cases, sudden massive occlusion of the major arterial tree from the origin of the common iliac to the bifurcation of the popliteal (Case 1), or nearly complete blockade of the main and collateral arteries at the root of the extremity (Case 2) may account for the observed severity of the ischemic changes.

The rigidity of the extremity and the stiffness of the joints are perhaps the most striking and characteristic features of this syndrome. This sign was never observed by the author,[6, 7] nor was it ever reported by others in cases of acute arterial occlusions. The painful myopathy involving several groups of

Fig. 1.

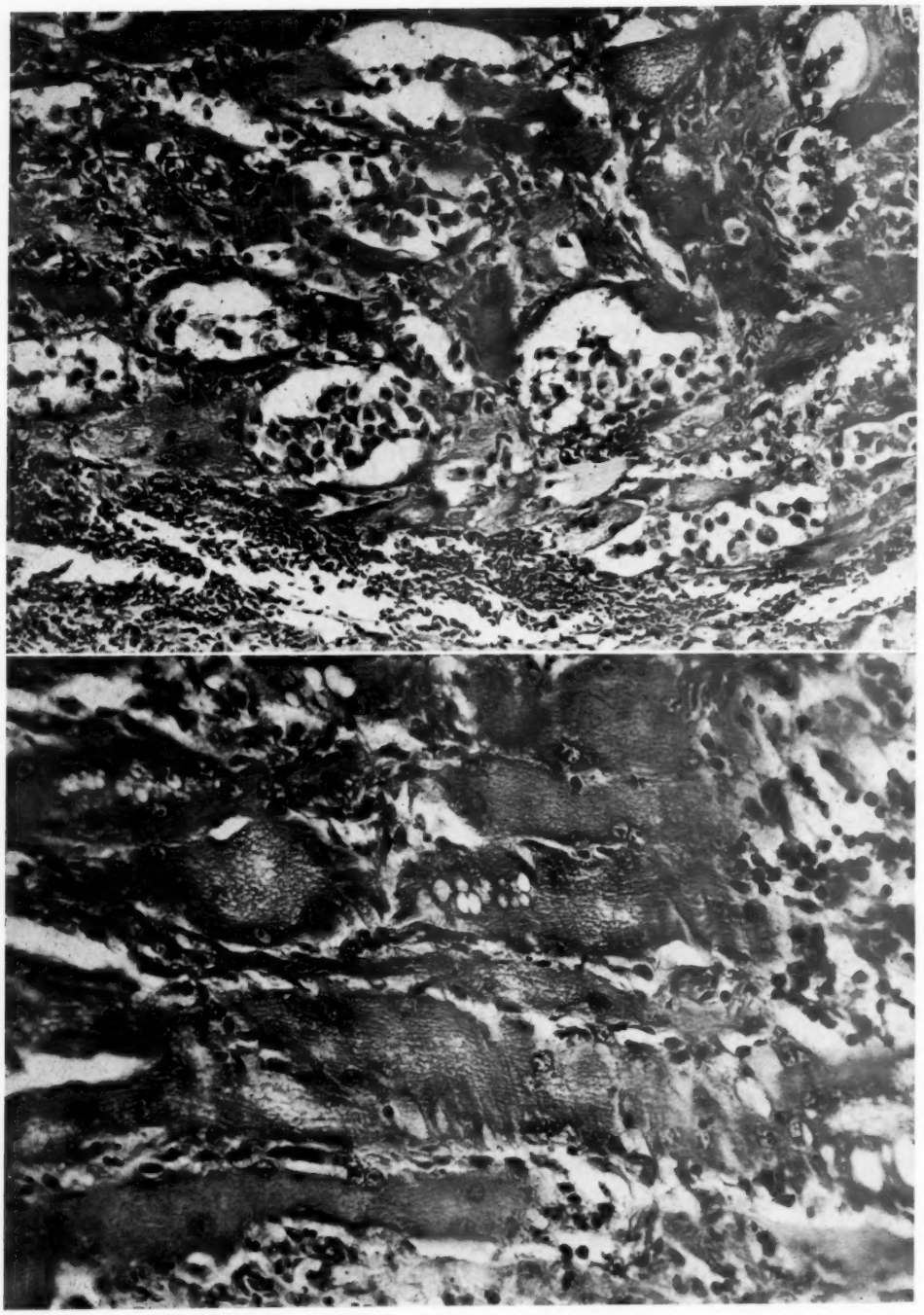

Fig. 2.

Fig. 1.—Muscular necrosis with loss of sarcoplasm. Note cellular infiltrates with histiocytes and occasional leukocytes. (×250, reduced ⅓.)

Fig. 2.—Sarcolemmal proliferation and regeneration of muscular fibers. (×400, reduced ⅓.)

muscles may account for this sign. Stiffness of the joints appeared so pronounced that its presence in association with an acute arterial embolism should evoke the possibility of ischemic myopathy and myoglobinuria. Indeed, it was found in both cases many hours before other clinical and laboratory findings disclosed the nature of the underlying pathology.

Edema of the extremity displayed characteristics not unlike those of iliofemoral thrombophlebitis. Massive swelling occurred within 18 to 24 hours after the clinical onset of the arterial occlusion. In the first case it involved the entire extremity although the swelling of the thigh was more pronounced than that of the leg. In the second case only the hip, thigh, and upper third of the leg appeared swollen. In both patients the involved areas were tense, swollen, and tender. The edema had a woody consistency and was nonpitting. This finding led to the diagnosis of massive venous thrombosis, superimposed on the arterial occlusion. The association of coldness and cyanosis seemed to lend further support to this diagnosis. However, postmortem findings in Case 1 and operative findings in Case 2 revealed complete absence of venous thrombosis in both instances. Moreover, in Case 2, re-exploration of the vessels 22 and 42 hours after the original embolectomy revealed the muscles of the hip and thigh to be tremendously swollen and pale with absence of subcutaneous edema. These operative findings, by disclosing the muscular lesions, helped to rule out the diagnosis of thrombophlebitis.

Pathogenesis.—The severity of the pain, rigidity of the extremity, and massive edema can all be correlated with the sudden biochemical and structural alterations in the skeletal muscle, which occurred as a result of the acute arterial occlusion. There is little doubt that these clinical and pathologic changes were the direct result of the embolism, since they were all confined to the extremity suddenly deprived of its arterial supply. The release of myoglobin and its renal excretion is ascribed to muscular damage and is thought to be an index of necrosis. A brief review of the microscopic muscular and urinary data of our 2 cases and their comparison with similar findings observed in conditions other than arterial embolism may further our understanding of the present syndrome.

Muscular Findings.—In both cases, at the time of the embolectomy (6 to 8½ hours after onset), gross appearance of the muscles of the hip, thigh, and leg did not reveal any apparent abnormality. In Case 2, however, 22 and 42 hours later, re-exploration of the vessels afforded examination of the muscles and showed them to be tremendously swollen and pale. In this connection, it might be of interest to mention that Carlstrom[4] in 1931 described an equine paroxysmal myoglobinuria syndrome in which the iliopsoas and quadriceps femoris appeared also edematous and pale, a syndrome which was apparently caused by thrombosis of the abdominal aorta. In 1945, Bywaters and Stead[3] reported a case of thrombosis of the femoral artery in a woman 63 years of age in whom muscle necrosis was associated with myoglobinuria. None of the characteristic clinical signs noted in our 2 patients were encountered in this case. The progressive onset of this thrombotic occlusion may account for its contrast with the clinical picture seen in the embolic occlusions.

The microscopic studies are based on specimens taken 10 days (Case 2) and 12 days (Case 1) after onset. Foci of loss of striation and of sarcolemmal nuclei of muscular fibers were recorded in both cases. In Case 2, there was in addition evidence of regeneration of muscular fibers. These morphologic changes resembled those described by others[1, 9] of various etiologies in myoglobinuria except that in our cases necrotic areas were perhaps more extensive. Had biopsies been taken at various intervals, a picture of chronologic and quantitative morphologic changes could have aided in the interpretation of the above late findings.

Urinary Findings.—It is generally accepted that myoglobinuria is dependent on myoglobin release from necrotic muscle.* There is no agreement, however, on whether muscle necrosis is the cause or the result of myoglobin liberation. Nevertheless, in traumatic muscle injury ("crush syndrome"), irreversible cellular damage, release of myoglobin, and myoglobinuria are the accepted sequence of events.

It is of interest to note that in our cases myoglobinuria appeared within 10 to 12 hours after the acute arterial occlusion, while the edema of the muscles occurred much later. In this connection, it might be interesting to raise the question of whether edema of the muscle occurred as a result of myoglobin release or whether the morphologic change was unrelated to this biochemical alteration of the muscular fiber and could be ascribed only to an ischemic phenomenon.

Duration and intensity of the myoglobinuria differed in the 2 cases. While in Case 2 the pigment disappeared within 4 to 5 days, in Case 1 it lasted until the death of the patient, 12 days after embolectomy. The cause of death in this latter case was the acute tubular necrosis ("myoglobinuric nephrosis"). It is likely that from its onset the magnitude of myoglobin liberation in Case 1 was such that it promoted the precipitation of protein and pigments in the tubules thus leading to renal shutdown.

Strenuous walking shortly after clinical onset of the embolism in Case 2 may have been a contributing factor to the myoglobin release, since physical exercise is known to precipitate attacks of idiopathic paroxysmal myoglobinuria.[9] The exact cause of myoglobin discharge from an ischemic muscle remains, however, unknown. While Bywaters and Stead[3] suggested a similarity of mechanism between traumatic myoglobinuria and that of arterial occlusion based on 1 case, there is no sufficient evidence to support such a contention. The experimental work of Brooks[2] and Clark[5] on ischemia of muscle reveals vastly different morphologic changes from those observed in crush injury.

Further experience is obviously necessary for a better understanding of this syndrome. It is hoped that awareness of such a condition may lead to routine analysis of urine or muscle biopsies in acute arterial occlusions and may further the understanding of this hitherto unrecognized complication and its possible prevention.

*If myoglobinuria always reflects the presence of muscle necrosis, it is surprising that it was never reported in cases of gangrene of the extremities.

SUMMARY AND CONCLUSIONS

1. Two cases of arterial embolism of the lower extremity associated with massive ischemic myopathy and myoglobinuria are reported.

2. Clinically, there were 4 characteristic manifestations: (a) excruciating pain; (b) severe and extensive ischemia of the tissues; (c) rigidity of the extremity with stiffness of the joints, and (d) massive edema.

3. The widespread ischemic myopathy of the extremity is the probable underlying cause of the severity of the local signs.

4. Myoglobinuria was found in both cases and may account for the fatal tubular necrosis (''myoglobinuric nephrosis'') in one patient.

5. Routine search for myoglobinuria and muscle biopsies in arterial embolism may uncover some unsuspected forms of this unusual syndrome.

The postmortem and microscopic findings in Case 1 were reported by Dr. S. H. Zuber, and the microscopic findings in Case 2 by Dr. D. Burdman, Department of Pathology. The myoglobin determinations were made by Dr. H. Horowitz and Dr. J. Javid, Department of Hematology.

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EVALUATION OF EXPERIMENTAL MYOCARDIAL REVASCULARIZATION OPERATIONS BY AMEROID CORONARY ARTERY CONSTRICTION

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IT has been shown by Litvak,[5] Duchesne,[2] and Deliyannis[6] that Ameroid constrictors placed around the origins of the anterior descending and circumflex branches of the left coronary artery results in the death of the majority of control animals, due to narrowing of the major coronary vessels by the expanding casein plastic. Death of the animals seems to occur when a critical point of narrowing is reached for two major vessels supplying the left ventricle. The average survival time of 36 animals was 20 days, and ranged from 3 to 59 days. It is not possible to state at what stage of coronary artery narrowing death occurs when one artery alone is involved. When both of the two major left coronary arteries are narrowed simultaneously, however, there does appear to be a point of critical narrowing beyond which death of the animal may occur at any time. A study of a scattergram plotting the percentage of anterior descending and circumflex occlusion by Ameroids is shown in Table I. It should be noted that no animal died when there was less than 40 per cent occlusion of the two major arteries.

Death and myocardial infarction represent truly objective evidence about which there can be no dispute. Any procedure, medical or surgical, which prevents death from Ameroid constriction of the anterior descending and circumflex branches of the left coronary artery probably supplies and distributes sufficient oxygenated blood to replace that denied the heart muscle due to coronary artery narrowing and obstruction.

The effectiveness of different revascularization procedures in preventing Ameroid coronary artery constriction death and myocardial infarction was studied by Mahanti for the following revascularization operations: (1) the Beck I operation, (2) cardiopneumopexy with lingular pulmonary artery ligation, (3) cardio-aortic Ivalon tube implantation, (4) internal mammary artery implantation, and (5) partial coronary sinus ligation.

Each operative procedure was performed after Vaseline-coated Ameroid constrictors had been placed around the origins of the anterior descending and the circumflex arteries at the same operation (Fig. 1). Thus, as the anterior descending and circumflex arteries are gradually narrowed, the left ventricle is

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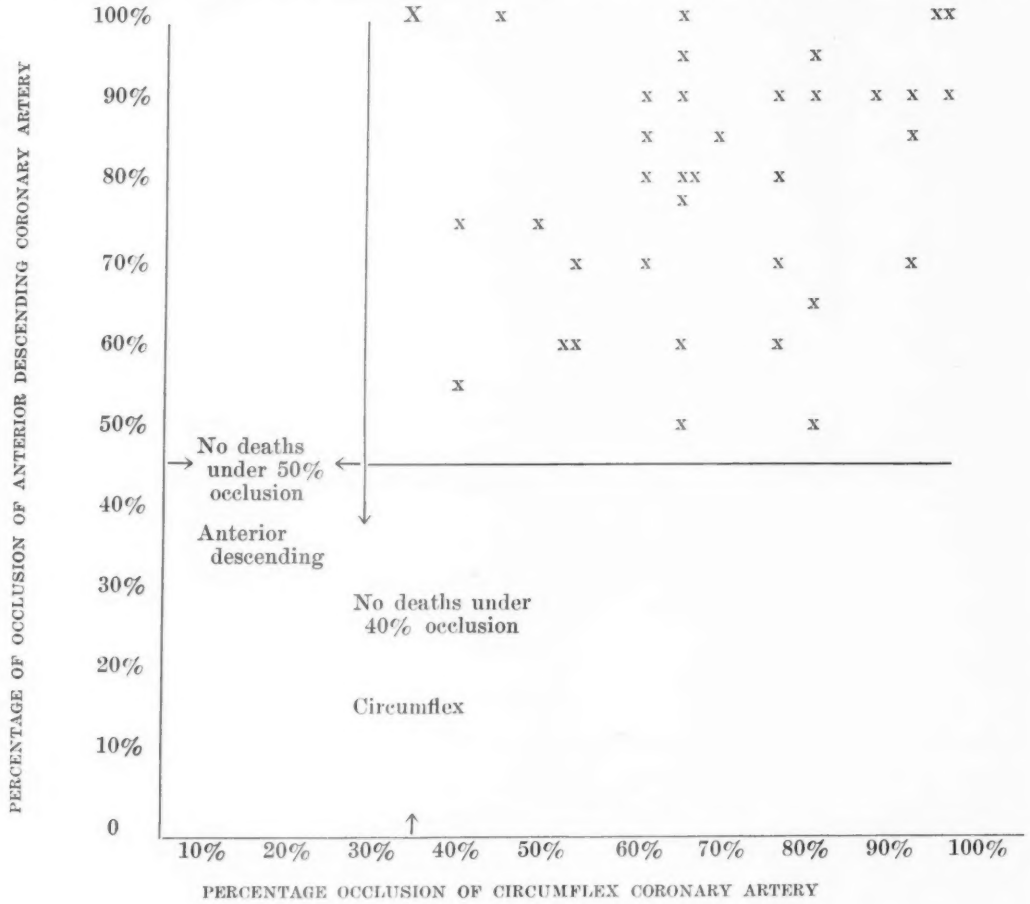
slowly made ischemic and the revascularization procedure is given an opportunity to form new pathways through which oxygenated blood reaches the left ventricle from sources other than the occluded or narrowed coronary arteries.

METHOD OF STUDY

The hearts of the various animals that died or were sacrificed for study were injected with Schlesinger mass. The anterior descending and circumflex arteries were cannulated distal to the Ameroids in all animals, and Schlesinger mass injected through these cannulas in the control and Beck I animals. In those animals with other operative procedures, Schlesinger mass was injected first through the pulmonary artery of the lingula, the Ivalon tube graft, and the internal mammary artery, respectively, for each series. An x-ray was taken

TABLE I. DEGREE OF ANTERIOR DESCENDING AND CIRCUMFLEX CORONARY ARTERY CONSTRICTION BY AMEROID SLEEVES IN 36 ANIMALS OUT OF 38 THAT DIED FROM MYOCARDIAL ISCHEMIA



to outline the extent of the anastomoses. When the injection of the pulmonary artery, the Ivalon tube graft, or the internal mammary artery failed to fill the left ventricular network, the injection was continued through the cannulas in the anterior descending and circumflex arteries. All hearts after injection were

unrolled and re-x-rayed to determine the extent of homocoronary and intercoronary anastomoses. These have been recorded as 0 to ++++. The position of the septal branch take-off in reference to the constricting Ameroid on the anterior descending branch was noted, as well as its origin from the left main coronary artery or the circumflex artery.

Histologic Studies.—

Coronary arteries: After the injection of Schlesinger mass, all hearts were fixed in formalin. After fixation, the steel-jacketed Ameroid constrictors were removed from the coronary arteries and sections were taken proximal, through, and distal to the points of Ameroid constriction. The extent of coronary artery constriction was studied, and the degree of narrowing of each artery recorded as a percentage of constriction of the original lumen.*

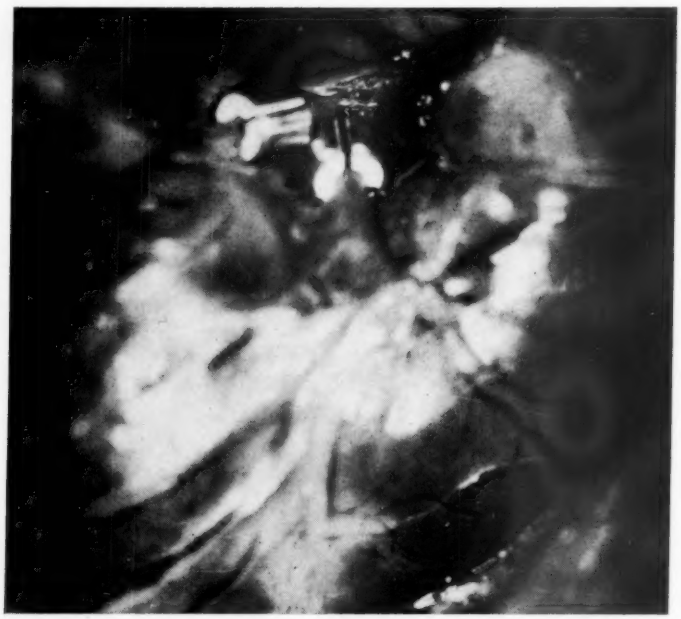


Fig. 1.—Shows Ameroid constrictors around the origins of the anterior descending and circumflex coronary arteries.

Angiographic Studies.—The coronary circulation and extracardiac blood channels were outlined by angiographic studies which were made in four different groups of living animals, namely: (1) coronary angiograms of animals with normal coronary arteries; (2) coronary angiograms made in control animals that had had coronary arteries constricted by Ameroid constrictors (these were done in order to co-relate, if possible, the degree of functional narrowing with that which was proved to be present on histologic observation); (3) angiograms in animals that had undergone internal mammary artery implantation, partial coronary sinus ligation, and (4) Ameroid coronary artery constriction

*Pathologic studies of the degree of coronary artery occlusion were performed by Dr. A. C. Guha, Assistant Professor of Pathology, under the direction of Dr. G. C. MacMillan, Professor of Pathology, McGill University.

(in these animals the radiopaque material was directed along the left subclavian artery, and down the implanted internal mammary artery in order to visualize mammary coronary anastomoses).

Control Series (10 Animals).—The anterior descending and circumflex arteries were dissected in 10 animals, and Vaseline-coated Ameroid sleeves were placed about their origins. None of the control animals lived longer than 41 days, and none died under 16 days after application of the coronary artery constrictors. The average survival time was 26 days. In not one of these 10 hearts was it possible to demonstrate extensive arteriolar connections between the right coronary artery and the left myocardial arteriolar network.

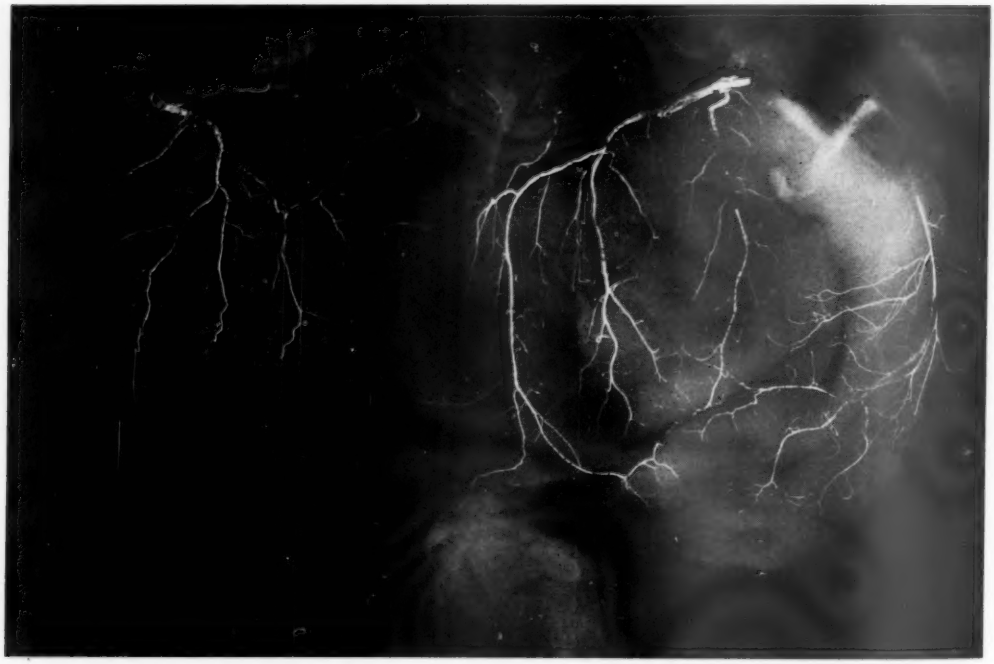
In Animal 153, a coronary arteriogram was obtained and showed the right coronary artery with no dye passing from the aorta through the circumflex, and very little into the anterior descending artery (Fig. 2). Postmortem roentgenogram Schlesinger mass injection studies of the same animal's heart showed only

Fig. 2.—Coronary arteriogram in control animal No. 153, in which Vaseline-coated Ameroid constrictors only have been placed around the anterior descending and circumflex coronary arteries. Note the visualization of the right coronary artery, none of the circumflex, and very little of the anterior descending branch.

one intercoronary anastomosis between right and left coronary arteries (Fig. 3). In this animal, histologic studies taken through the anterior descending coronary artery showed it to be 85 per cent occluded at the site of Ameroid constriction, and the circumflex branch of the left coronary artery was 90 per cent occluded (Fig. 4). The data shown for Animal 153 is characteristic of all control animals studied.

Cardio-aortic Ivalon Tube Implant, With Ameroid Coronary Constrictors.—In this operation a piece of Ivalon is fashioned into a tube. One end of the tube is anastomosed to the descending aorta, and the other end buried within

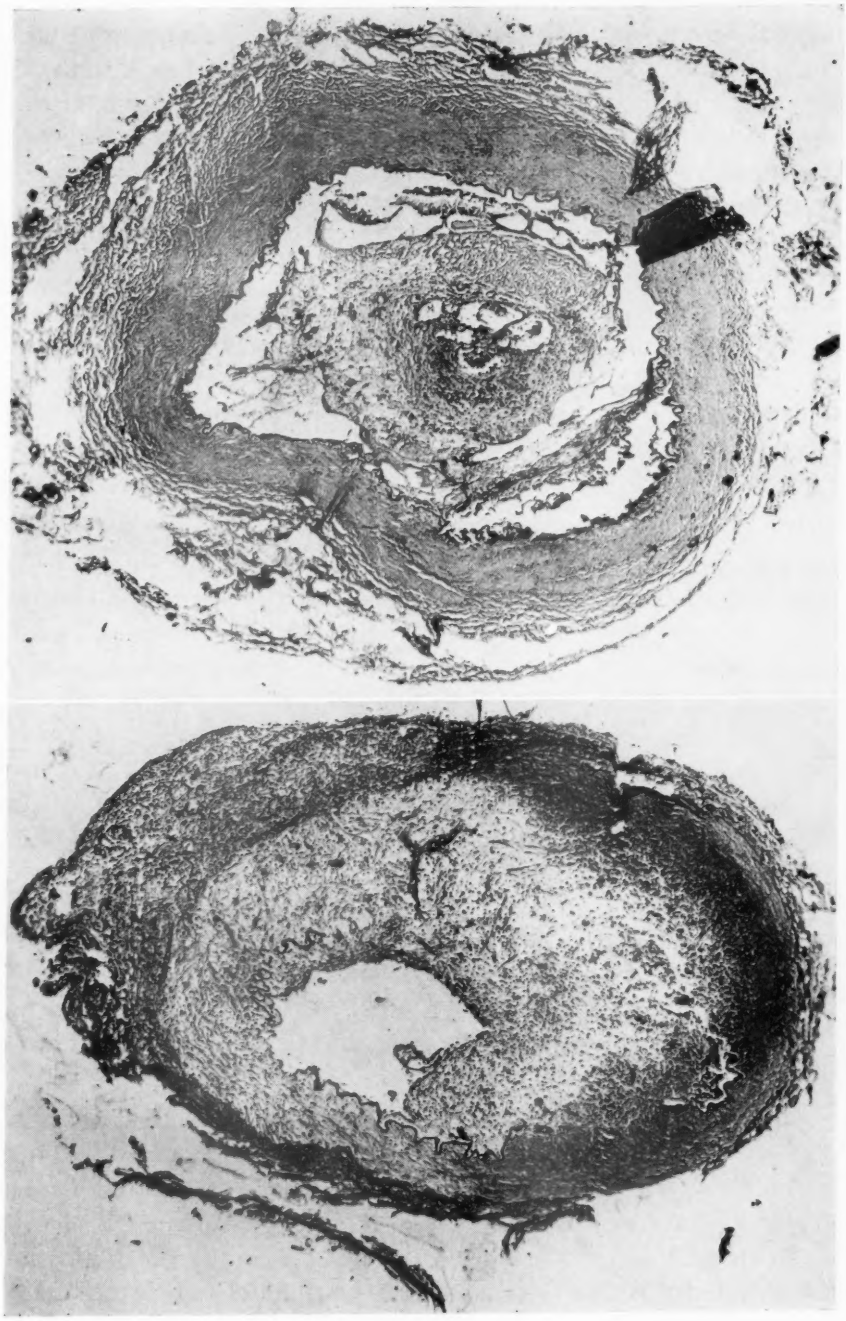
A.



B.

Fig. 3.—*A*, Control animal No. 154. X-ray study of intercoronary anastomoses by Schlesinger mass injection. Note the presence of only one intercoronary anastomosis between the right and left coronary arteries (posteroanterior view). *B*, Same as *A*, showing the heart unrolled. Note only 1 plus intercoronary anastomosis and no more than one homocornary artery anastomosis.

A.



B.

Fig. 4.—Photomicrograph of sections taken through site of Ameroid placement on coronary arteries. *A*, Microscopic section through the anterior descending branch within the Ameroid. Note the obstruction of the lumen and thickened media with chronic inflammatory cells. This was considered to be 85 per cent occluded. *B*, Photomicrograph of section taken through the circumflex artery at the site of Ameroid constriction, showing 90 per cent occlusion of the lumen.

a myocardial tunnel with its distal end open. At the same operation, Vaseline-coated Ameroid constrictors were placed around the origins of the anterior descending and circumflex arteries. The purpose of this experiment was to attempt to reproduce the mechanical stimuli that occur when a tunnel is made in the left ventricular myocardium and a bleeding internal mammary artery is introduced. It has often been stated by others that any operative procedure on the heart stimulates intercoronary anastomoses. This argument has been used to explain survival from experimental anterior descending coronary artery ligation and the disappearance of anginal pain after a revascularization procedure in the treatment of human coronary artery disease.

In this series, 9 animals with cardio-aortic Ivalon tube implant combined with Ameroid constriction of the anterior descending and circumflex arteries were operated upon. None of these animals survived: 8 of the 9 were dead within 41 days. Animal 314 survived for 102 days and showed ++ intercoronary and homocoronary anastomoses. In only one animal was the Ivalon tube graft patent. There were no communications between the implanted graft and the vessels of the myocardium.

Cardiopneumopexy.—There have been a few active proponents of this procedure, which has been performed in various ways. The technique used is the same as that followed by Harken in the treatment of human cases of coronary artery insufficiency, namely, phenolization of the left ventricular surface and the medial surface of the lingula. In addition, the pulmonary artery to the lingula was ligated at the same operation to encourage bronchial coronary artery anastomoses, as suggested by Liebow. Each animal also had Vaseline-coated Ameroid constrictors placed around the origins of the anterior descending and circumflex arteries. Each heart was studied, as previously outlined. In addition, the lingula of the pulmonary artery was injected antegrade with Schlesinger mass, in an attempt to outline communications between the vessels of the lingula and the left coronary circulation. Seven of the 9 animals died between 14 and 60 days (average 29 days). Two animals, Nos. 25 and 94, were sacrificed for study after 175 and 139 days, respectively. In No. 25, the degree of arterial occlusion was 90 per cent for the anterior descending and 40 per cent for the circumflex. For No. 94 it was 85 per cent for the anterior descending and 65 per cent for the circumflex. When these hearts were studied by Schlesinger mass injection, intercoronary anastomoses were shown between the right coronary and the left coronary arteries distal to the point of Ameroid coronary constriction. These intercoronary anastomoses, although present in some animals, were not as extensive in those animals that died. In no instance did the Schlesinger mass injected through the lingular branch of the pulmonary artery reach the heart (Fig. 5). In every instance the junction between the lingula and the left ventricular muscle was examined microscopically, but in none was there any evidence of vascular communication between the lung and the heart. The two were separated by thickened avascular epicardium with chronic inflammatory reaction (Fig. 6).

Beck I Operation.—In this operation, the epicardium of the left ventricle was scraped off, using the Beck scraper, as well as the endothelial layer of the

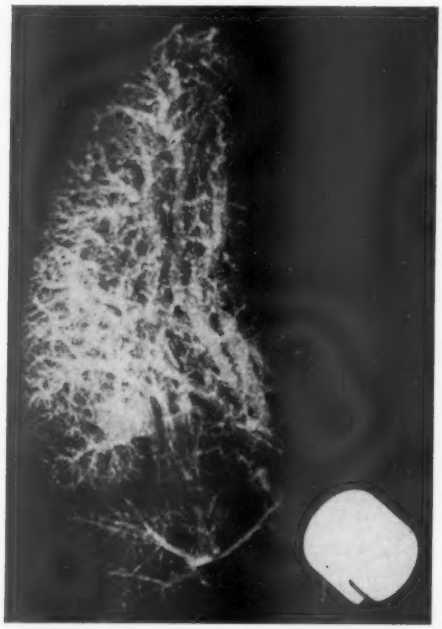


Fig. 5.—Animal 120. Died 60 days after placing Ameroid constrictors on the two main left coronary arteries and applying the lingula to the left ventricle, after phenolization of the two surfaces. The lingular artery was injected with Schlesinger mass. Note the absence of communication between the injected lung vessels and the vessels of the left ventricle which lie to the right of the photograph.

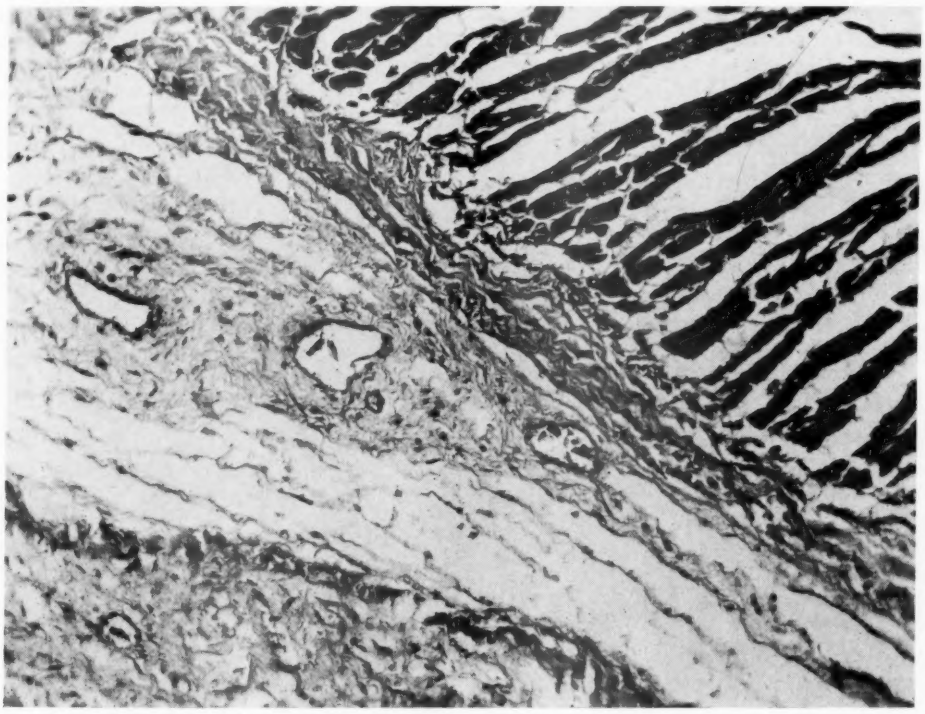


Fig. 6.—Photomicrograph showing a section through the junction between the lingula and the left ventricular muscle. Note the thickened epicardium with chronic inflammatory reaction. There are no vascular communications between the graft and the myocardium.

pericardium. Asbestos powder was sprinkled upon the denuded myocardium and pericardial fat pads sewn on to the left ventricle; the coronary sinus was partially ligated over a 3 mm. Beck probe, and Vaseline-coated Ameroid sleeve constrictors were placed around the origins of the anterior descending and circumflex arteries.

Nine of the 10 animals died between 19 and 88 days, an average of 28 days. Two animals only showed more than average intercoronary anastomoses. One of these animals was No. 314 which survived 88 days; the other, No. 313, was sacrificed after 190 days and extensive intercoronary anastomoses were found. In none of the animals was it possible to prove communications between the pericardial and myocardial vessels, nor was there evidence to indicate that partial ligation of coronary sinus resulted in the development of large enough intercoronary anastomoses to prevent death. Sections through the contiguous heart and pericardial surfaces showed a thickened pericardial layer infiltrated with chronic inflammatory cells and fibroblasts. It was not a picture of granuloma and there were no vascular communications.

Internal Mammary Artery Implantation and Partial Coronary Sinus Ligation Plus Coronary Ameroid Constrictors.—An internal mammary artery implanted into the ventricular myocardium starts budding in 12 days and forms mammary coronary anastomoses between 4 and 6 weeks. Six months are required for these to develop into large enough channels to deliver sufficient blood to protect the entire left ventricle when its two major coronary arteries are narrowed or occluded. In addition, 6 months are required to develop and grow sufficient intercoronary anastomoses to permit extracardiac blood introduced into the anterior ventricular wall through an implanted internal mammary artery to be distributed throughout the ventricular myocardium to its posterior portion. Since partial coronary sinus ligation is said to increase intercoronary collaterals, it was decided to combine internal mammary artery implantation with coronary sinus partial ligation in order to obtain rapid distribution of the blood brought to the left ventricle through an implanted internal mammary artery. The combined operations were performed on 10 animals which had Ameroid constrictors placed around the anterior descending and circumflex branches of the left coronary artery at the same operation. Seven of the 10 animals survived 6 months or more. All had open, soft, pulsating internal mammary arteries. Six or 7 showed satisfactory mammary-coronary anastomoses. These were demonstrated by injecting the implanted internal mammary artery with Schlesinger mass. For example, in Fig. 7, an x-ray of the left ventricle of Animal 168 shows how the entire coronary artery system of the left ventricle was filled by the Schlesinger mass, followed by a branch of the right coronary and its tributaries through an implant which had been placed in the left ventricle 236 days previously. The same heart is shown in Fig. 8 after it had been unrolled and an x-ray taken to show the extent of the distribution of the Schlesinger mass which had reached the heart through the implanted internal mammary artery.

Fig. 7.—Photographic reproduction of x-ray of Animal 168, sacrificed 236 days after internal mammary artery implantation and Ameroid constriction. Schlesinger mass entered the internal mammary artery and filled the entire left ventricular arteriolar system, as well as part of the right ventricle (Mahanti).

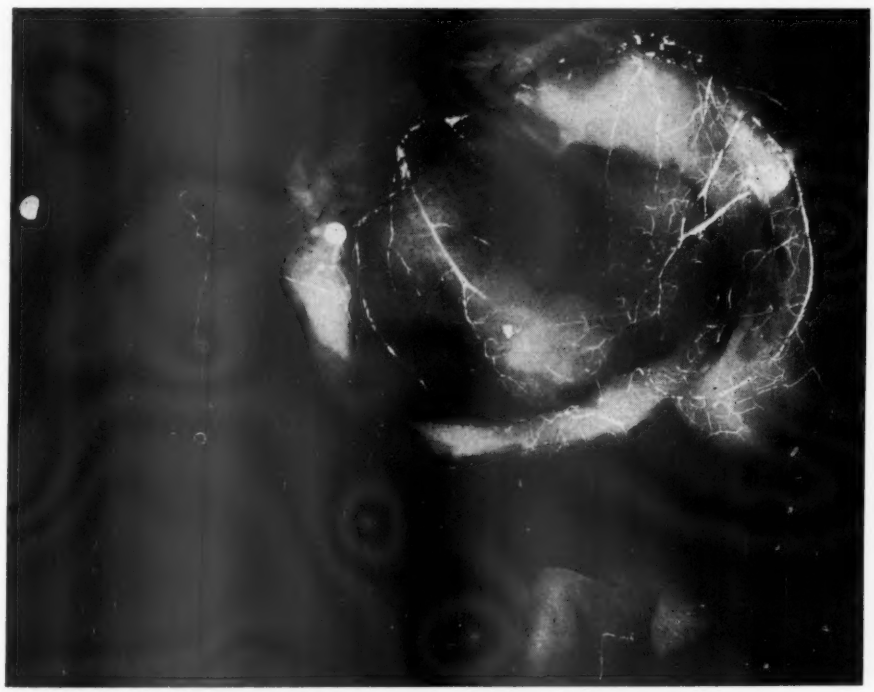


Fig. 8.—The same heart as shown in Fig. 7, except that the x-ray was taken after the heart had been unrolled.

A. *B.* *C.*

Fig. 9.—An angiocardiogram made of Animal 151 by injecting a radiopaque dye through the subclavian artery and internal mammary artery in the living animal, and taking rapid serial x-ray prints (Mahanti and Grainger). This animal had been operated upon 214 days previously, at which time Ameroid constrictors were placed on the two main left coronary arteries, and internal mammary artery implantation carried out, with partial ligation of the coronary sinus. *A*, Angiocardiogram of the heart of Animal 151. Note how the radiopaque dye has entered the internal mammary artery which is lying within the left ventricle. *B*, Angiocardiogram of Animal 151 showing the radiopaque dye filling the implanted internal mammary artery and entering the coronary vessels lying within the myocardium. The radiopaque dye has filled the major coronary arteries in retrograde fashion back to the origin of the left coronary artery. *C*, Angiocardiogram of Animal 151 showing that the radiopaque dye has not only entered the left ventricle through the implanted internal mammary artery, but has traversed the coronary arteries and capillaries to emerge from the partially constricted coronary sinus.

*Angiocardiography.**—The hearts of some of these animals were examined by angiocardiographs which were made by injecting 90 per cent Urokon into the left subclavian and implanted internal mammary artery. A good example of such an angiocardiograph is that which was carried out on Animal 151. This animal was examined 214 days after internal mammary artery implantation, sinus ligation, and the placing of Ameroid constrictors around the anterior descending and circumflex branches of the left coronary artery. In the serial x-rays taken at 6 films per second, the radiopaque dye can be seen travelling down the implanted internal mammary artery and entering the anterior wall of the left ventricle through branches of the implanted internal mammary artery (Fig. 9, *A*). Quickly the radiopaque dye flows out into the surrounding left ventricular arterioles and coronary arteries, which were filled in a retrograde manner, back to the origin of the left coronary artery (Fig. 9, *B*).

It should be observed that the narrowed or blocked main left coronary arteries were bypassed, and note how the radiopaque dye mixed with blood in a beating heart reached all parts of the left ventricle and apparently traversed the capillary bed, since it is seen to fill the partially constricted coronary sinus (Fig. 9, *C*). In this particular animal histologic sections showed the anterior descending artery to be 100 per cent occluded, and the circumflex artery 75 per cent occluded (Figs. 10 and 11).

DISCUSSION

The Ameroid coronary artery constriction test in the animal is an extremely severe test of any method of treatment for coronary artery insufficiency. Prior to this test there have been many series studied with regard to the protective value of a given operative procedure against sudden occlusion of the anterior descending branch of the left coronary artery. In the experimental animal, a few animals with implanted internal mammary arteries have survived ligation of the anterior descending branch and of the left circumflex artery. This does not seem to have been true for other revascularization procedures.

A summary of Mahanti's work concerning the value of various revascularization procedures in protecting against death from Ameroid constriction of the two major coronary arteries is shown in Table II. All the 10 control animals were dead within 41 days after Ameroid placement. It is interesting to note that 8 out of 8 bilateral internal mammary artery ligations with subclavian ligation also died in an average of 25 days. Cardiopneumopexy appears not to have been of much benefit: 7 of 9 animals died, and the 2 animals surviving showed good coronary anastomosis between the right coronary branches and the arterioles of the left ventricle. Neither of these 2 animals which were sacrificed showed any evidence of vascular communication between the lung and the myocardium. Since there was no extracardiac system of blood introduced, the survival of these two hearts was most probably due to blood coming from the right coronary artery.

Cardio-aortic tube graft implants simulated in every way an internal mammary artery implant, except for the fact that no blood was carried into the heart

*The radiographic studies of the various revascularization procedures were performed by Dr. F. A. Grainger, of the Department of Radiology, Royal Victoria Hospital.

TABLE II. AMEROID CORONARY ARTERY CONSTRICTION SURVIVAL TEST OF SURGICAL REVASCULARIZATION PROCEDURES

VASELINE-COATED AMEROIDS ON ANTERIOR DESCENDING AND CIRCUMFLEX BRANCHES OF THE LEFT CORONARY ARTERY	NUMBER OF ANIMALS	WEIGHT (POUNDS)	DEAD	AVERAGE SURVIVAL (DAYS)	RANGE OF SURVIVAL (DAYS)	NUMBER SACRIFICED AFTER 5 OR 6 MONTHS OR LONGER FOR STUDY
1. Control	10	43-50	10	26	16- 41	–
2. Bilateral internal mammary ligation and subclavian ligation	8	42-50	8	25	–	–
3. Cardiopneumopexy	9	43-52	7	28	14- 60	2
4. Cardio-aortic Ivalon tube implant	9	–	9	34	16-102	–
5. Beck I	10	44-52	9	26	16- 88	1
6. Internal mammary artery plus coronary sinus partial ligation	10	42-50	3 (2 blocked arteries)	32	20- 22	7 All arteries open with anastomoses in 6 animals

Fig. 10.

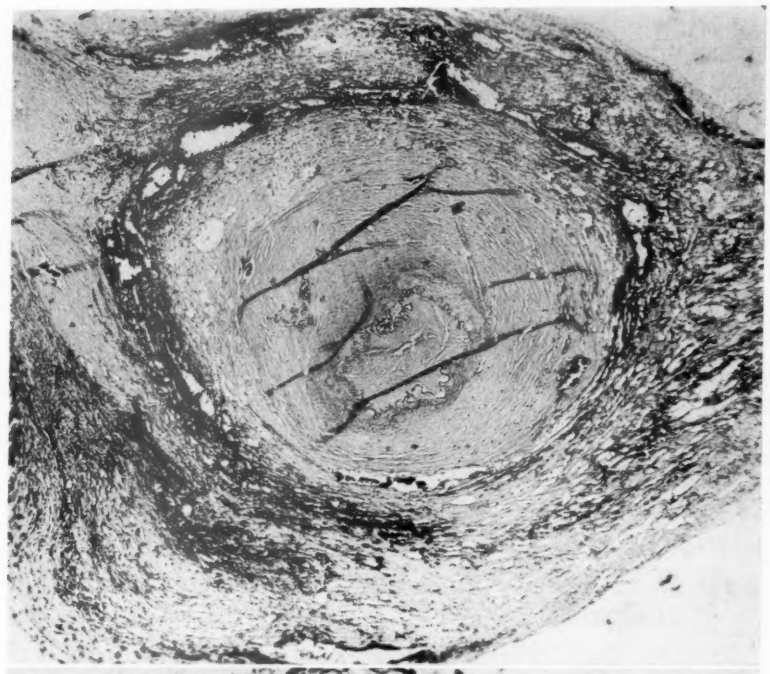


Fig. 11.

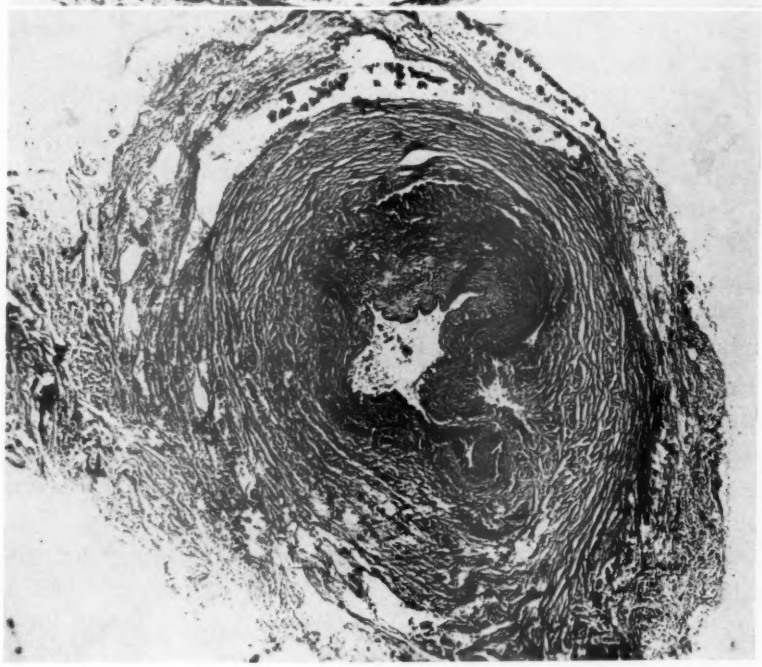


Fig. 10.—Animal 151. Photomicrograph of anterior descending artery at site of Ameroid constriction, showing 100 per cent occlusion of the lumen.

Fig. 11.—Animal 151. Photomicrograph of circumflex artery at the site of constriction, showing 100 per cent occlusion of the lumen.

through the tube grafts. Nine out of 9 of these animals died between 16 and 102 days, averaging 34 days. Obviously, since there was no extracardiac blood introduced to replace that lost by the narrowed left coronary arteries, the animals died. Certainly the making of a tunnel did not stimulate the formation of extracardiac blood supplies, nor did it open up satisfactorily large enough anastomoses between the right and left coronary systems to relieve the ischemia caused by Ameroid coronary artery constriction.

Beck I Operation.—It was hoped that in these experiments evidence would be obtained to show that the Beck I operation stimulated sufficient intercoronary channels to distribute what blood was entering the heart evenly and, therefore, prevent Ameroid coronary artery constriction death. Such was not the case, since 9 out of 10 animals died between 19 and 88 days, averaging 28 days of life, and one animal only showed the extensive anastomosis referred to so frequently by Beck[1] and claimed by him to be established by partial coronary sinus ligation. This animal was sacrificed after 190 days. There were numerous arteriolar connections between the right coronary artery and the left ventricular arteriolar system. Again, as in the other procedures, there was absolutely no evidence of extracardiac and myocardial vascular connection, so that one must presume that this one animal survived due to the patent right coronary artery. This failure of the Beck I operation to protect against narrowing or occlusion of the two main left coronary arteries is not hard to understand, since Beck has never claimed his operation to do more than distribute what blood is present evenly throughout the myocardium.

Internal Mammary Artery Implantation Combined With Coronary Sinus Ligation.—In this series there were 10 animals in whom the internal mammary artery was implanted, the coronary sinus partially ligated, and Ameroids placed around the anterior descending and circumflex branches of the left coronary artery. Seven of these animals survived beyond 6 months, and 6 of these had extensive mammary-coronary anastomoses. One of the 6, Animal 168, showed intercoronary anastomoses between the left and right coronary arteriolar systems of sufficient size to permit the Schlesinger injection mass introduced through the implanted internal mammary artery to fill the left ventricular arteriolar network. Thus in 5 animals it can be reasonably assumed that the internal mammary artery alone was responsible for the survival of the left ventricle and, therefore, of the animal. The addition of partial coronary sinus ligation seems to have increased the long-term survival rate of the internal mammary artery implant when the two major left coronary arteries are very markedly constricted by Ameroid constrictors. Of course, this is a small group of animals. This result was expected, particularly if partial ligation of the coronary sinus does what it is claimed to do, namely, open up intercoronary anastomoses so that the blood introduced by the implanted internal mammary artery into the anterior surface of the left ventricle is rapidly distributed throughout the left ventricle, and can reach the posterior surface of the heart to replace the blood that does not reach this area due to the narrowed or occluded circumflex artery.

From Mahanti's study it seems quite clear that the only operative procedure in his series which affords protection against progressive anterior descending and circumflex artery occlusion is the internal mammary artery implant operation and coronary sinus ligation. A reduction of 50 per cent or more in the size of the two main left coronary arteries appears to be a serious matter in the animal. The distribution of any blood that is left is apparently not sufficient, and it is thus necessary to obtain blood either from an extracardiac source, such as an implanted internal mammary artery, or from the nonconstricted right coronary artery, in order to prevent death.

Undoubtedly there will be critics who will ask about the position and the state of the septal branch of the left coronary artery. In 48 animals the position of the septal branch was carefully recorded. It originated 29 times from the anterior descending artery, 11 times from the main left coronary artery, and 8 times from the circumflex artery. However, in only 3 of the 48 animals was an Ameroid constrictor placed proximal to the septal branch take-off. In the 3 cases where the Ameroid constrictor was placed proximal to the origin of the septal branch, one was in the Beck I series; one in the cardio-aortic tube graft series, and one in the cardiopneumopexy. All 3 animals died at about the same time as the control group animals—a 24-day average.

In 45 animals the septal branch arose proximal to the points of Ameroid occlusion and was therefore untouched by the Ameroid constrictor. Obviously this artery may be considered as an important source of blood supply to relieve myocardial ischemia brought about by major left coronary artery narrowing in the animal. All controls that died or lived and all implanted internal mammary arteries that lived or died had open septal branches, so that the presence of this open vessel proximal to the point of coronary artery constriction was not a factor in the survival of the internal mammary artery implant-coronary sinus ligation in animals.

CONCLUSIONS

The method of slowly narrowing the anterior descending and circumflex arteries by Ameroid plastic constrictors affords an excellent but severe test of revascularization procedures. The death of the animal occurs when 50 per cent or more of the lumina of both major left coronary arteries are simultaneously constricted. The presence of an open septal branch and right coronary artery does not prevent death unless anastomosis between the right coronary arteriolar and left arteriolar branches occurs. Such intercoronary anastomosis developed of sufficient size in 4 animals of a series, and may have been a factor in preventing the death of these animals. It occurred in the following frequency and distribution: 1 in 10 times in the Beck I operation, 2 in 9 times in the cardiopneumopexy procedure, and 1 in 10 times in the internal mammary artery and coronary sinus ligation procedure.*

In the entire series of 56 animals, 10 controls and 46 operated upon, the only operative procedure which prevented death was the internal mammary

*About 10 per cent of normal dogs' hearts show intercoronary anastomoses between the right and left coronary arteries.

artery implantation and partial coronary sinus ligation. In a previous report, Duchesne showed that the internal mammary artery implantation alone, when given time, would likewise prevent an animal's death from Vaseline-coated Ameroid coronary artery constriction. It is clear that even though there may be adequate distribution of a diminished quantity of blood entering the left ventricle through narrowed coronary arteries, this in itself is not enough to prevent myocardial infarction. It is necessary to introduce extra coronary arterial blood, or blood from the right coronary artery, in order to replace that arterial blood prevented from passing into the heart through narrowed or blocked coronary arteries.

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EXPERIMENTAL GRADUAL CORONARY ARTERY CONSTRICTION BY AMEROID CONSTRICTORS

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THE peculiarity of human coronary artery disease has made evaluation of any method of treatment, medical or surgical, most difficult to assess. The same has been true of the experimental animal. In order to evaluate experimental methods of revascularization it seemed necessary to have a reliable method of coronary artery narrowing and occlusion. Such a method must consistently cause the death of control animals with or without infarction. Death or myocardial infarction represent objective evidence which is hard to negate so that any reliable method of producing coronary artery occlusion places in the hands of the experimenter a useful tool that can be utilized for objective evaluation of various revascularization procedures.

CORONARY ARTERY CONSTRICTION BY AMEROID CONSTRICTORS

The Ameroid constriction method for narrowing and occluding coronary artery vessels was developed by Litvak in our experimental laboratories, details of which have been published.[1, 2] Ameroid is a plastic product made of casein which swells when it absorbs water. The coronary artery Ameroid constrictors are made from a bar of Ameroid in which a central lumen has been drilled to precision size. Communicating with this lumen from the periphery there is a slot large enough to permit a coronary artery to be slid along the slot into the central lumen. The Ameroid is encased in a steel jacket which diverts Ameroid swelling centrally so as to narrow the central lumen (Fig. 1). A dry Ameroid placed in saline reduces its central lumen from 3 mm. to 1.65 mm. in diameter in 16 days and to 1.57 mm. in 26 days. Ameroids which are coated with Vaseline absorb water more slowly and consequently swell less rapidly. Such Ameroid sleeves reduce their central lumina from 3 mm. to 1.98 mm. in 32 days and to 1.8 mm. in 54 days (Fig. 2). The slowly contracting Vaseline-coated coronary artery Ameroid constrictors have been used in order to give more time for the heart to re-establish its circulation either naturally or by means of surgical revascularization procedures.

METHODS OF CONTROL

Coronary artery Ameroid constricting sleeves are made in the same shop to precision size in a large number (Fig. 3). These are placed in a box and

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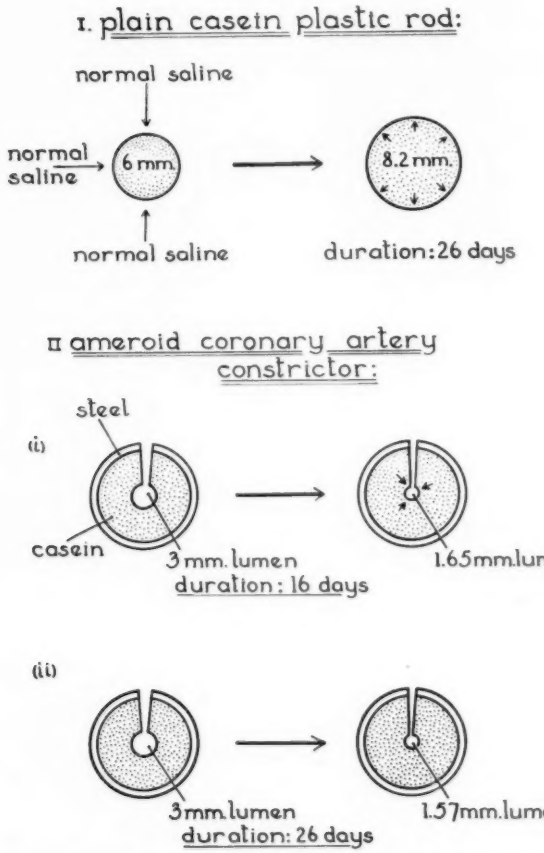


Fig. 1.—Casein bar with central lumen and slot housed in steel jacket which prevents eccentric expansion as Ameroid swells after water absorption.

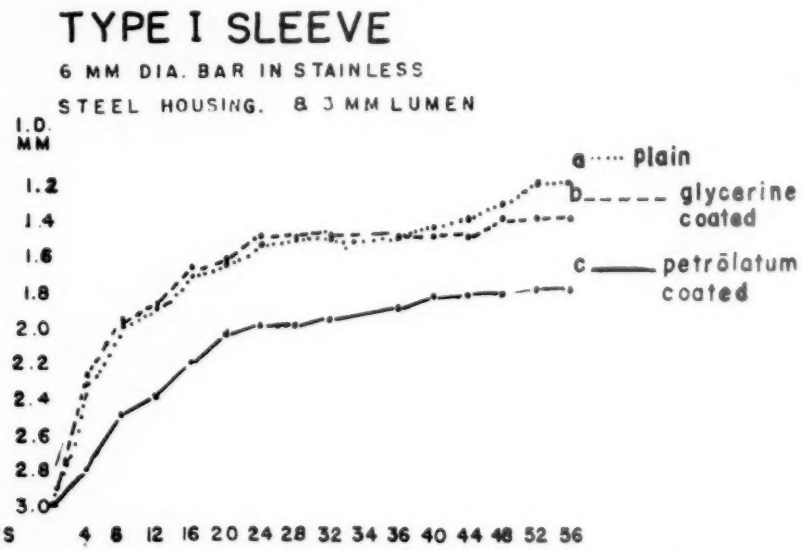


Fig. 2.—Rate of closure of lumen in Ameroid. Vaseline-coated Ameroids absorb water more slowly thus constrict coronary artery around which it is placed at a slower rate.

thoroughly mixed. Prior to using they are placed in a desiccator from which they are removed and put in a jar containing Vaseline.

METHOD OF STERILIZATION

Litvak recommended placing the jar containing Vaseline and Ameroids in a hot water bath for one hour in order to obtain uniformity of Vaseline impregnation of the Ameroid material. Autoclaving of the Ameroid sleeves, although satisfactory, appears to result in a lesser degree of Vaseline impregnation of the Ameroids and therefore a more rapid swelling and consequent narrowing of the central lumen. This variation in sterilization accounts for the differences noted in the survival time in series reported by different workers in our laboratory (Table I).

TABLE I. SURVIVAL RATE FOLLOWING VASELINE AMEROID CONSTRICTION OF THE MAIN LEFT CORONARY ARTERIES

SERIES	NUMBER OF ANIMALS	AVERAGE WEIGHT	DIED	SACRIFICED DUE TO ILLNESS	AVERAGE SURVIVAL TIME (DAYS)	RANGE OF SURVIVAL TIME (DAYS)	SIX MONTHS PLUS SACRIFICED
Delyannis	13	38 lbs. (30-44)	10	3	19	11 to 43	0
Korman	11		11	0	15	3 to 59	0
Mahanti	10	45 lbs. (43-50)	10	0	26	16 to 41	0
	34		31	3	20	3 to 59	

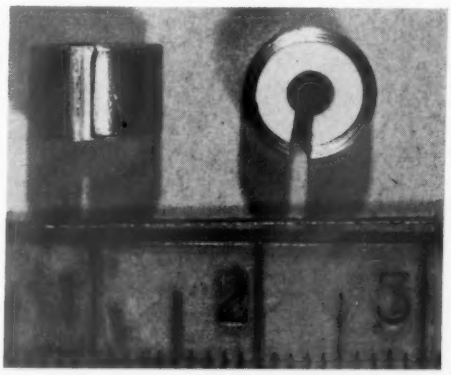


Fig. 3.—Complete Ameroids with steel sleeves ready for application to anterior descending and circumflex coronary artery.

SIZE OF DOGS

In order to occlude coronary arteries of approximately the same size, dogs ranging between 40 and 50 pounds are used.

ALTERNATE OPERATIONS

In order to exclude the variable factors of weather, season, and so forth in the recovery of the animal, operations have been carried out so that a control operation is followed on the same or the next day by a revascularization procedure.

STANDARD CONTROL AMEROID OPERATION

The left thorax is opened and the pericardium is incised anterior to the left phrenic nerve from base to diaphragm. A ligature is passed through the tip of the left atrial appendage for traction purposes. Three cubic centimeters of 1 per cent procaine hydrochloride is injected under the epicardium with a 24-gauge needle over the area where the left coronary artery branches into the anterior descending and circumflex arteries. A small incision is made in the epicardium overlying this area; a blunt probe is inserted and used to separate the epicardium from underlying fat and blood vessels for a distance of approximately 2 cm. down the anterior descending and circumflex branches, and then incised. The underlying coronary trunks are dissected free from surrounding

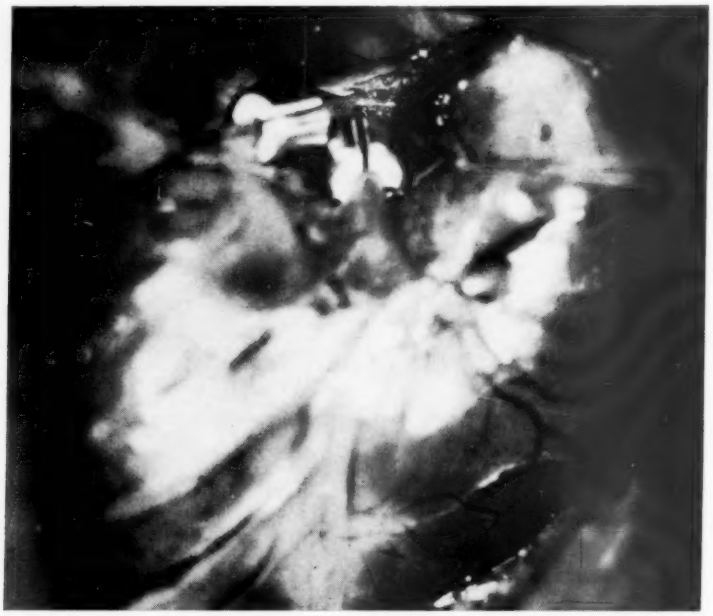


Fig. 4.—Shows coronary artery Ameroid constrictors in situ around the origins of the anterior descending and circumflex branches of the left coronary artery.

tissues by doubly ligating all small vessels with 3-0 plain catgut in the proposed area of casein plastic sleeve application. A loop of linen ligature is passed around the anterior descending and circumflex branches and utilized to maintain traction distally for a few seconds while the casein plastic sleeves are slipped onto the origins of the anterior descending and circumflex branches of the left coronary artery. After the Ameroids are on the artery and are rotated so that the slotted opening faces the operator, no adjustment of the steel jacket in order to obtain a better fit around the coronary artery is permitted (Fig. 4).

STUDIES

Studies have been made of each heart after death, as follows: (1) injection of Schlesinger mass into the left coronary artery, (2) x-ray showing distribution of Schlesinger mass and degree of coronary occlusion, (3) cross sections of the

left ventricle studied for gross infarction, (4) microscopic sections for detailed infarction, (5) sections through anterior descending and circumflex arteries proximal to them and distal to the site of Ameroid constriction, and (6) presence of aberrant coronary arteries or septal branches proximal to the constricting Ameroids.

GRADUAL CONSTRICTION OF THE TWO MAJOR LEFT CORONARY ARTERIES

Previous survival experiments relied mainly on sudden occlusion of the anterior descending coronary artery at its origin followed by circumflex coronary artery ligation. The statistics of survival for the former vary greatly in different hands. Few revascularization procedures protected against sudden occlusion of the circumflex artery. By gradual occlusion of the two major coronary arteries it is hoped that revascularization methods may have time to work. The effect of placing Vaseline-coated constrictors around major coronary arteries is shown in Table I for 34 control dogs operated on by three different workers. The combined average time of survival for 34 animals was 20 days with the time of death varying from 3 to 59 days. These animals died suddenly or had to be sacrificed due to illness. There were no 4 to 6 months' survivors. Of the 34 animals 31 (91 per cent) died naturally and 3 (9 per cent) were sacrificed due to illness. Histologic studies performed upon the hearts of these animals show that many animals died from myocardial infarction without complete occlusion of either coronary arteries. There appeared to be a stage of narrowing at which the animal's life became endangered. Animal caretakers have learned to detect prodromal symptoms of impending death, for example, a few days prior to their death some animals would lie on their backs whimpering and refusing to move, showing all the evidence of anginal pain. Others, 3 to 4 days prior to death, appeared listless and were not interested in food or exercise. In some, however, there was no warning, particularly in large animals which frequently died suddenly after eating, fighting, or running. Rapid examination of their hearts under these conditions showed they had died of ventricular fibrillation usually without myocardial infarction.

CRITICAL POINT OF CORONARY ARTERY NARROWING

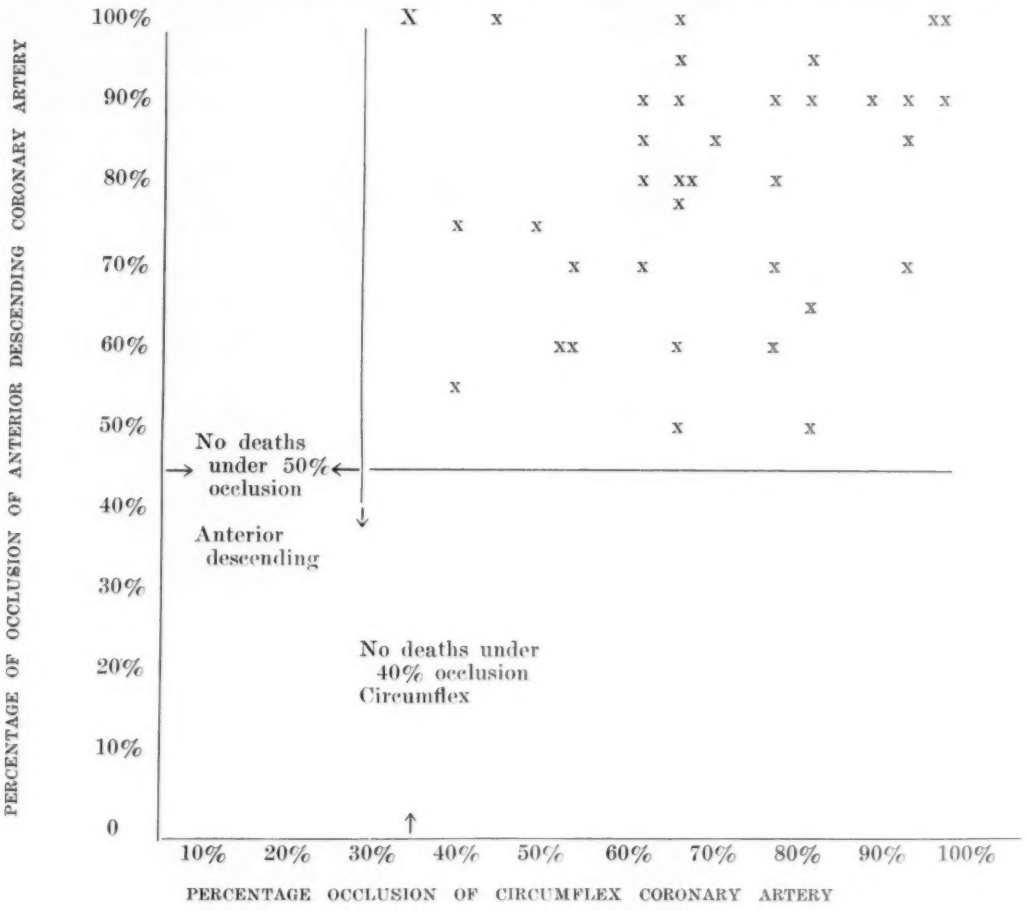
From a study of our many animals it has become obvious that as the Ameroid constrictors contract the coronary arteries, a point of critical narrowing is reached at which, or beyond which, death may result. The establishment of such a critical point of coronary artery narrowing experimentally may have great significance in the selection of patients suffering with coronary artery heart disease for revascularization surgery, since human coronary arteries may be satisfactorily visualized by the image intensifier.

A study by Mahanti's* experiments shown in Table I, in which 38 animals are listed and the extent of Ameroid narrowing of the anterior descending and circumflex branches of the left coronary arteries are recorded. It is interesting to note that no animal died unless both major coronary arteries had a reduction

*Complete details of this work is in course of publication.

of 40 per cent or more of their lumina. A scattergram of 36 of 38 animals that died is shown in Table II, and it is seen that 8 (22 per cent) died when there was between 60 to 70 per cent or less occlusion of both arteries. In fact, in one animal, death occurred with 55 per cent anterior descending occlusion, and 45 per cent circumflex occlusion. Of the 36 deaths, there were only 5 animals in

TABLE II. DEGREE OF ANTERIOR DESCENDING AND CIRCUMFLEX CORONARY ARTERY CONSTRICTION BY AMEROID SLEEVES IN 36 ANIMALS OUT OF 38 THAT DIED FROM MYOCARDIAL ISCHEMIA



which one or both coronary arteries had become completely blocked. Thirty-one (78 per cent) died with narrowed but completely patent coronary arteries. There were 2 animals of the 38 that survived in spite of 90 per cent narrowing of the anterior descending (Animal 175), and 70 per cent narrowing of the anterior descending with 100 per cent occlusion of the circumflex (Animal 313). In both these animals there were extensive arteriolar or larger anastomoses between the right coronary artery and the left ventricular arteriolar bed.

From this work certain facts emerge, namely: (1) The critical point of coronary artery narrowing occurs when the two major coronary arteries of the left ventricle are reduced by 40 per cent or more. (2) Death occurs in 95 per

cent of the animals in which the two major left coronary arteries are narrowed by Ameroid constriction. (3) Of the 36 animals that died, 31 (78 per cent) died with both major coronary arteries narrowed but completely patent. (4) The two surviving animals appeared to do so by virtue of the development of intercoronary anastomoses between the normal right coronary artery and the arterioles of the left ventricle.

With these experimental facts in mind, let us examine human coronary artery disease, particularly with reference to the selection of patients for revascularization surgery.

From the evidence it is reasonable to assume that if the two major coronary arteries of the left ventricle show 50 per cent or more narrowing of their lumina, then that particular patient is in danger of sudden death. Attempts to make this estimation should be done as frequently as possible by coronary arteriography. In human coronary artery heart disease, the critical point of coronary artery narrowing may be even less than 50 per cent, since the disease causes irregularities of the intima which, in addition to narrowing, favor occlusion of the coronary artery lumen by thrombi. The point of critical narrowing of at least two coronary arteries which has been found to be true in the animal, may only apply to younger patients most of whom are coroner's cases due to the suddenness of their deaths. In this younger group of patients, a sudden demand for blood distal to points of coronary artery narrowing occurs frequently, and may result in sudden death without coronary artery occlusion. In the older group of patients who die more often in hospitals it is more common to find arterial occlusion due to old or fresh thrombus. In either case, the visualization of coronary artery lumina through coronary arteriography may show vessels narrowed by 50 per cent or more, in which event, certainly in the younger patients under 55, such measurements would point to the necessity for corrective coronary artery surgery.

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HIGH OUTPUT BUBBLE OXYGENATOR WITH VARIABLE OXYGENATING CHAMBER FOR CARDIAC BYPASS

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SEVERAL oxygenators using the principle of mixing oxygen bubbles with blood for extracorporeal gas exchange are presently in successful clinical use.[2-5] The limitations of the bubble principle in available equipment are concerned with two factors. Primarily, the rate of flow which can be attained without danger of delivering undispersed bubbles and thereby producing air emboli is such that in high flow perfusion, particularly in adults, such equipment is utilized at a point very near or at its maximum tolerance within which it can safely perform. The problem of delivering high volumes has, in the case of one type of bubble oxygenator, been met by using two oxygenators in parallel which, of course, increases safe flow but at the same time increases the amount of blood needed, the labor of preparation, and perhaps the hazard of the perfusion.

The second limitation of bubble oxygenation is inherent in the efficiency of the bubble-mixing principle in bringing about gas exchange. In existing bubble oxygenators, the problem of oxygenation of the blood is entirely adequately met. Discrepancies in the removal of carbon dioxide, however, are ignored within wide limits and compensated for in the face of serious discrepancy by the addition of carbon dioxide to the oxygen gas supplied.

It is the purpose of this presentation to describe a new bubble oxygenator which satisfies these and certain other requirements which appear to be important.

REQUIREMENTS OF ADEQUATE EQUIPMENT

One of the requirements of good equipment is that the degree of oxygenation and carbon dioxide elimination be varied in proportion to the volume of blood being perfused. To have entirely reproducible results, the equipment itself must be variable in some manner to calibrate it to the rate of perfusion. Passage of oxygen bubbles through venous blood is a very efficient method of producing gas exchange in the hemoglobin.[1] The problem is not one of oxygenation of blood, but of controlling both the amount of oxygenation and the degree to which carbon dioxide is removed. When carried out to excess, bubble oxygenation will bring about an excessive removal of carbon dioxide. At the same time, saturation of the blood plasma with oxygen may lead to danger if the oxygen is later released as the blood is pumped into the body.

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The removal of the gas phase of the gas-blood mixture must be as completely and abruptly accomplished as possible. Unless this is accomplished in short order, after blood has passed through the chamber in which oxygen and blood is mixed, the gas will remain to disturb seriously the calibration of extent of oxygen mixing with the rate of the required perfusion. Thus, the requirement of rapid removal of bubbles or defoaming is added to the obvious requirements that it must be completely done and that once blood has been freed of bubbles, it should not be allowed to become foamy again through splashing or dropping as it passes on through the equipment.

The defoaming of blood is usually accomplished by contact with a foam-dispersing surface produced by the application of silicone A to the walls of the equipment. A requirement of a good bubble oxygenator should be that there is a minimum contact between the blood-gas mixture and the antifoam surface. If large amounts of antifoam are required, or if the surface is a large one over which the perfusion must pass, the solid Antifoam A may become suspended in the perfused blood and produce damage by a mechanical if not a toxic effect in the patient.

DESCRIPTION OF EQUIPMENT

The new bubble oxygenator satisfies these requirements: high flow rates without danger of gas embolism, variability of gas-blood contact in proportion to the flow rate being used, and minimum contact with antifoam substances. Avoidance of dangerous degrees of trauma to the blood was found to be unexpectedly easy with high flow rates because many of the considerations that permit delivery of blood with stable chemistry also provide that the blood receives careful handling.

In the course of the development of this equipment, a good deal of attention was paid to the ease with which the equipment could be prepared and sterilized. Simplification was not especially required, except where it could be attained without any loss of efficiency. Therefore, the equipment has more parts, particularly in the defoaming area, than have most other bubble oxygenators.

The oxygenator consists of four areas. Blood is delivered into the area of mixing with oxygen bubbles from which it passes upward into a head which is the area of defoaming. After defoaming it flows downward through a delivery area into the reservoir which is inherent in the equipment.

OXYGENATING AREA

The oxygenating chamber is a vertical cylinder of stainless steel which consists of three parts, all of which are used in every perfusion. The volume of the oxygenating chamber is adjusted to one of four volumes, depending upon the rate of perfusion required. The variation is accomplished by the order in which the three cylinders are put together, and the level at which the blood delivery tube and perforated disk through which the oxygen is delivered are installed between various of the three tubes (Fig. 1).

DEFOAMING CHAMBER

The defoaming chamber encloses the upper part of the oxygenating chamber (Fig. 1, *A*). It consists of three cylinders resting on a stainless steel plate of special design, all contained within an outer collecting chamber which delivers the blood, suitably defoamed, into the area of transportation to the reservoir. The three internal cylinders are concentrically placed on the plate. Blood-oxygen mixture is received into the central one, and progressively passes into the outer cylinders through shallow notches cut in the bottom of each. As the

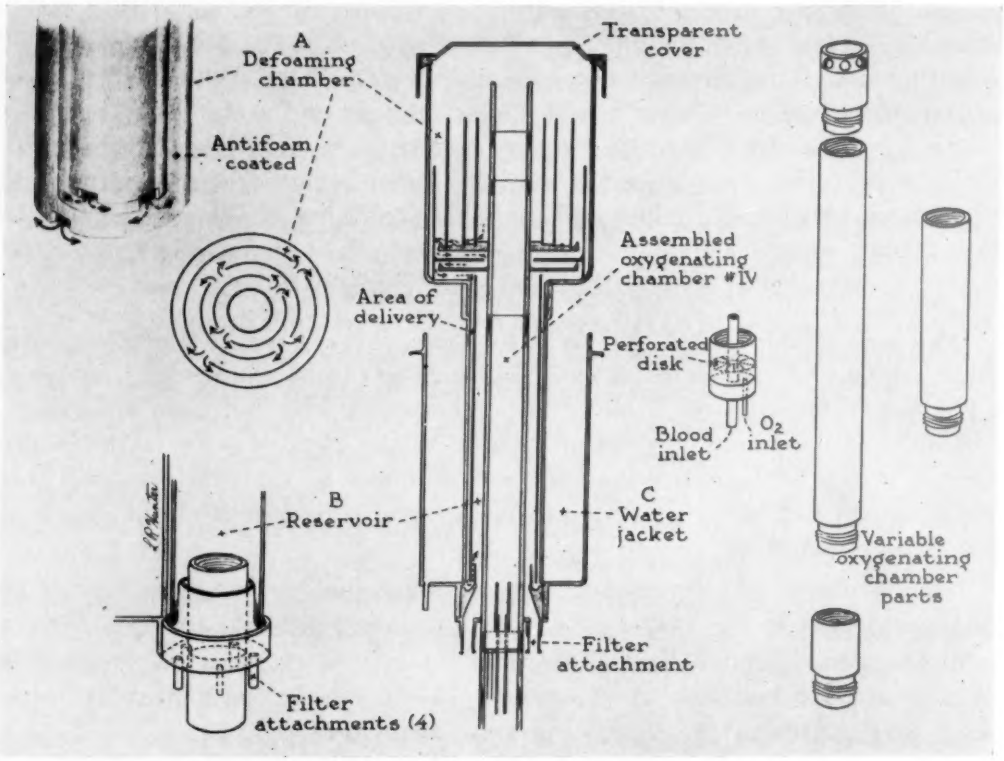

Fig. 1.—Cross-section of the oxygenator with the mixing and defoaming chambers and the base with its filter attachments. The arrangement of the openings between various cylinders of the defoaming chamber is shown. These openings provide for defoaming by "skimming" action and minimum contact with antifoam-coated surfaces.

blood passes from one to the other, only the solid blood unmixed with oxygen bubbles goes through these notches, the supernatant foam being skimmed by this manner of design. The surfaces of these cylinders are coated with antifoam. Blood does not flow over these coated surfaces, but rather the bubbles rise against the surfaces, utilizing only that area which is necessary to accomplish complete destruction of the bubbles. Minimum contact with antifoam, therefore, occurs for any rate of perfusion.

AREA OF DELIVERY

The defoamed blood is not permitted to fall into the reservoir, but rather passes down a narrow space $\frac{3}{16}$ inch in thickness formed in the periphery of

the reservoir chamber by the introduction of a second cylinder within the reservoir. This area immediately becomes full after starting the perfusion and thereafter permits a steady downward progression of the blood without splashing.

RESERVOIR

The reservoir chamber is relatively narrow, providing the greatest possible distance between the bottom from which blood is withdrawn to the upper surface of the blood within the chamber. The long narrow shape minimizes the volume of blood required in the reservoir during perfusion. This volume is not more than 500 ml. The method of withdrawal of blood from the reservoir is also, we believe, important. Minimum suction and trauma in withdrawal of blood and its immediate filtration are accomplished by using four openings at the bottom of the reservoir, each attached to a filter, thereby reducing both resistance and speed of passage of blood through each filter (Fig. 1, *B*).

The entirety of the area of delivery and the reservoir are enclosed in an outer shell of stainless steel which is a water jacket for heat exchange to maintain or cause rapid changes in the temperature of the blood passing through the equipment (Fig. 1, *C*). Inasmuch as the volume of blood required to charge this oxygenator can be kept at a minimum, it was thought desirable to have an immediate supply of blood available for replenishing, in case of need, the perfusion volume. A second cylindrical reservoir, having a volume of 6 L., is an auxiliary portion of the equipment. This is also provided with a water jacket to maintain the temperature of the blood which is held in reserve. Advantage was taken of this additional chamber by using it as a primary reservoir in initial loading of the equipment so that passage of blood through the oxygenating chamber would be minimized.

The final auxiliary equipment consists of the chamber into which blood is drawn as it is aspirated from the operative field during surgery. This intracardiac suction reservoir is filled from the operative field by suction maintained through attachment to any form of hospital suction equipment. In order that this blood may be returned to the oxygenator without interrupting the intracardiac suction, it is passed at intervals through the positive action of a pump from the bottom of the collecting chamber to the inflow of the oxygenator.

These auxiliary chambers and their connections are shown in relation to the assembled oxygenating equipment in Fig. 2.

RELATION OF DESIGN TO REQUIREMENTS

The most obvious factor in maintaining the oxygen and carbon dioxide contents of arterial and venous blood and the pH of blood delivered by an oxygenator is the adequacy of the perfusion. A perfusion of entirely properly treated blood in inadequate amount results in acidosis on the basis of development of fixed acids due to the low oxygen tension in the tissues.

A more important consideration in maintaining stable blood chemistry during perfusion is the relationship within the equipment between the volume

of blood per minute in the perfusion, the time that the blood stays in the mixing chamber in contact with oxygen, and the volume of oxygen which is passed through the mixing chamber. From a practical standpoint in a bubble oxygenator, these factors are best controlled through varying the size of the chamber in which the blood is mixed with oxygen in proportion to the rate of perfusion. It is quite clear that the same sized oxygenating chamber cannot be used to provide different rates of blood flow if stable chemistry is to be

Fig. 2.—Assembled oxygenating equipment with auxiliary chambers and their connections.

maintained. If a large oxygenating chamber is used for patients requiring small flow, the result will be hyperventilation. The blood delivered by the machine will be adequately or more than adequately oxygenated, but the CO_2 removal will be excessive and alkalosis will result. If, on the other hand, an oxygenating chamber of small size is used for a large patient requiring greater blood flow, there will be retention of carbon dioxide, acidosis, and insufficient oxygenation of the blood delivered.

Much work was devoted in the present development to the calculation, fabrication, and testing of oxygenating chambers of varying sizes which, when used for different flow rates, would maintain a stable arteriovenous difference in oxygen and in carbon dioxide together with prevention of pH changes during a period of perfusion. Inherent in such "ideal" chamber size for each flow rate was the fact that a unit volume of blood would remain in contact with the bubble stream of oxygen for approximately the same length of time in each chamber. Excessive exposures to the mechanical trauma of the passage of bubbles were therefore avoided and dangerous levels of plasma hemoglobin did not occur. An initial study was carried out to determine the flow rate of oxygen which would produce adequate oxygenation with the least amount of trauma. It was found that the passage of progressively larger amounts of oxygen through the same mixing chamber with unchanged blood flow produced increasing amounts of hemolysis. This relationship is shown in Fig. 3 which records the results of 12

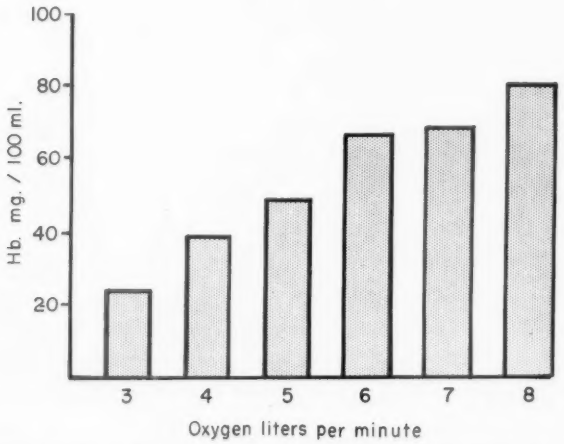

Fig. 3.—Results obtained by serum hemoglobin determinations on blood circulated through oxygenator at the rate of 1,700 ml. per minute for 40 minutes with each flow rate of O_2 through the chamber. During a constant perfusion flow the red cell hemolysis is a function of the volume of O_2 passing through the oxygenator.

consecutive experiments in which 100 per cent oxygen was passed through a mixing chamber together with a blood flow of 1,700 ml. per minute. When the oxygen flow was 3 L. per minute, hemolysis produced a plasma hemoglobin of 25 mg. per cent at the end of 40 minutes. A level of 80 mg. of hemoglobin per 100 ml. of blood was produced when 8 L. of oxygen per minute was passed through the same chamber for the same period.

After preliminary calculations, a variety of sizes of mixing chambers were used to determine what may be called "optimum blood flow." It was found that

a volume of 3 to 7 L. of oxygen per minute produced entirely adequate gas exchange in the various chambers using appropriate flows. Of the many sizes initially tested, four were selected for complete evaluation. The relative sizes and dimensions of these four chambers, referred to by the Roman numerals I, II, III, and IV are, respectively, 10, 16, 26, and 34 inches long with an internal diameter of 2 inches. The economical method of obtaining these variations in size by using three cylinders and a movable ring containing the blood and oxygen delivery tubes has been described. The oxygen diffusion disk contains 90 to 100 holes equal to lumen of a standard No. 24 gauge needle in diameter.

Oxygen flows of 3 L. per minute are used in chamber I, 5 L. per minute in chambers II and III, and 7 L. per minute in chamber IV. Respectively, the optimum perfusion with these oxygen flows are 400 to 900, 1,500 to 2,100, 2,800 to 3,500, and 4,300 to 5,200 ml. of blood per minute. The actual useful perfusion rates for which these oxygenator chambers may be used are much less critical. For the four the useful rate is 200 to 1,300, 1,300 to 2,400, 2,400 to 4,100, and 4,100 to 5,600 ml. per minute.

METHODS AND RESULTS IN TESTING CHAMBER SIZES

The data representing the testing of chambers I, II, and III were obtained in the experimental animal. Additional data on these three chambers and all of the data presented in relation to chamber IV were obtained in patients after sufficient confidence had been gained for the clinical use of the equipment.

Fig. 4 shows the result of using each chamber at a flow of 1,800 ml. per minute in 10 dogs of such size that this perfusion equalled 80 to 90 ml. per kilogram per minute. The graph shows the oxygen saturation, carbon dioxide level, the pH, and the serum hemoglobin level which resulted. During the experiment, each chamber was used in progressive periods of 15 minutes of perfusion; the samples were obtained at the end of each period. On the basis of these experiments, it was found that the most favorable levels resulted during the 1,800 ml. perfusion when chamber II was being used. Fig. 5 similarly shows the same blood chemistry determination using each chamber in sequence with perfusion of 2,600 ml. per minute (90 to 120 ml. per kilogram). These data indicate the use of oxygenator chamber III for this total flow rate.

Fig. 6 shows venous as well as arterial blood chemistry at the end of complete 1-hour perfusions in dogs using chambers II and III at the flow rate of 80 to 120 ml. per kilogram per minute (1,850 to 2,600 ml. per minute). At this rate of flow chamber II was found to maintain normal levels and good arteriovenous differences of oxygen, carbon dioxide, and pH. Chamber III at this flow showed the effect of hyperventilation.

The testing of the larger chamber, oxygenator IV, was carried out in clinical patients in whom perfusion rates of 4,100 to over 5,000 ml. were required. Table I shows the average blood chemistry in 6 patients obtained before, during, and at the end of perfusion. The average perfusion flow of 70 to 90 ml. per kilogram per minute was maintained for an average of 43 minutes. The arterial and venous pH remained essentially constant as did the oxygen and CO_2 content of the arterial and venous sides of the equipment.

TABLE I

AVERAGE BLOOD CHEMISTRY (6 PATIENTS)	OXYGENATER NO. IV						
	ARTERIAL			VENOUS			
	O_2 VOL. %	CO_2 VOL. %	pH	O_2 VOL. %	CO_2 VOL. %	pH	Hb MG. %
Control	17.4	52.0	7.38	11.8	56	7.30	
5 min.	17.8	48.4	7.52	12.4	54	7.42	30
15 min.	18.2	49.2	7.48	11.8	58	7.48	
30 min.	18.0	47.2	7.45	12.2	58	7.46	48
End perfusion	17.6	48.0	7.42	12.0	54	7.38	80

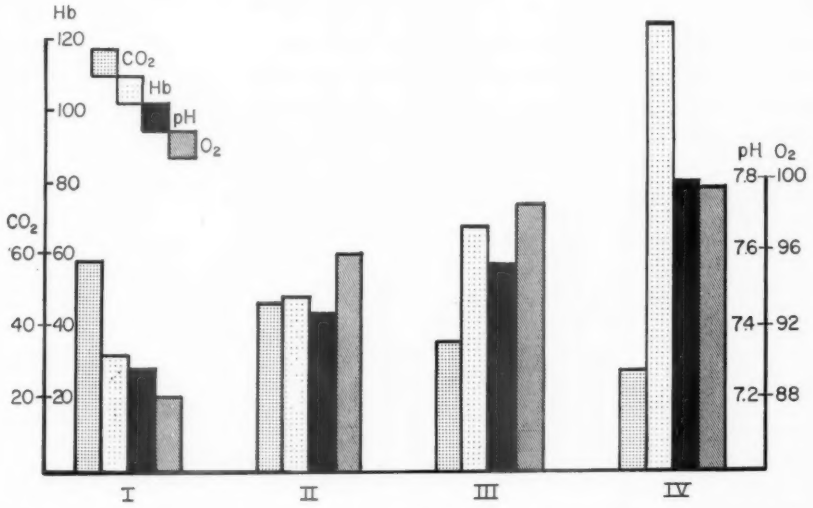

Fig. 4.—The arterial blood levels of pH, O_2, CO_2, and serum hemoglobin using perfusion flows of 1,300 to 2,400 ml. per minute. These values are optimal in the case of oxygenator chamber II. When a smaller oxygenator is chosen, acidosis results. On the other hand, the use of the larger chambers, III and IV, produces alkalosis due to hyperventilation and over-oxygenation.

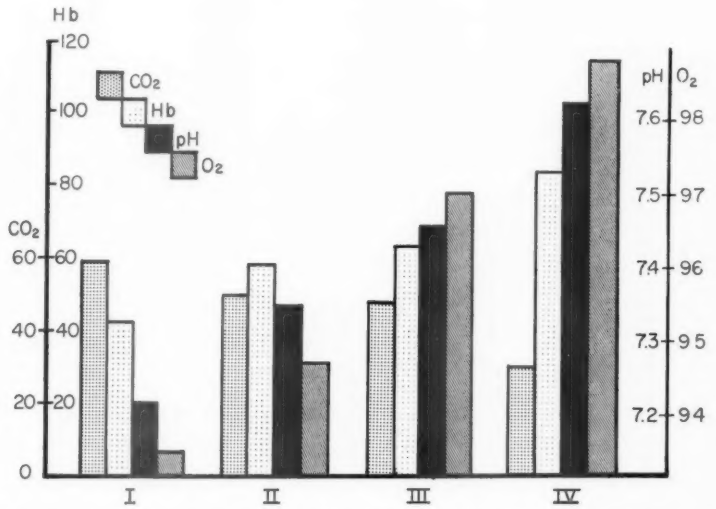

Fig. 5.—The perfusion conditions achieved with flows of 2,400 to 4,200 ml. per minute employing each oxygenator. Optimum results were obtained at the flow with chamber III.

Consideration was given to the possibility that better results might be obtained through the use of a mixture of oxygen and CO_2 instead of 100 per cent oxygen. A comparison of the use of pure oxygen with that of 95 per cent oxygen plus 5 per cent carbon dioxide is presented in Table II. This shows the data obtained in dogs using these gases with mixing chambers II and III. The rate of perfusion in each experiment was 1,850 to 2,300 ml. per minute which represented 80 to 100 ml. per minute per kilogram of body weight. Oxygenation was adequate both with pure oxygen and with the gas mixture. However, the gas mixture produced a significant acidosis and carbon dioxide retention with both oxygenator chambers. It is quite likely a larger oxygenator chamber used with this mixture might abolish the acidosis. This, however, would have resulted in overoxygenation of plasma and greater trauma to the blood cells. The investigation of use of gas mixture was abandoned early in our study.

TABLE II

	OXYGENATOR CHAMBER	ARTERIAL			VENOUS		
		O_2 VOL. %	CO_2 VOL. %	pH	O_2 VOL. %	CO_2 VOL. %	pH
100% oxygen	II	19.8	39.7	7.48	10.2	52.0	7.43
	III	22.2	35.8	7.58	11.4	48.3	7.54
95% oxygen + 5% CO_2	II	19.3	52.4	7.13	10.1	69.4	7.10
	III	22.9	46.3	7.24	11.7	68.3	7.19

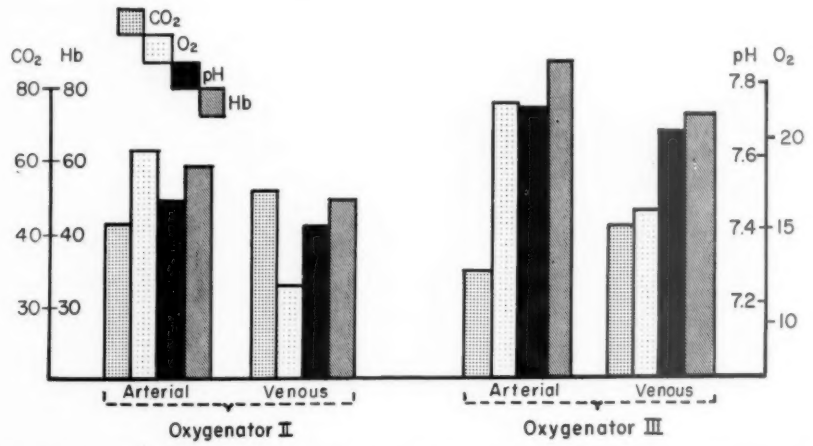

Fig. 6.—Arterial and venous contents of oxygen, CO_2, pH, and serum hemoglobin resulting from use of chambers II and III at flow rate of 1,800 to 2,600 ml. per minute. Hyperventilation and alkalosis resulted from use of chamber III.

Table III records the average of determinations of acid-base balance in 8 patients who were perfused by using oxygenator chamber IV at rates of 4,100 to over 5,000 ml. per minute. The minimum changes in the pH and CO_2 content of arterial blood are clearly evident. The buffer base which represents the concentration of bicarbonate and hemoglobin ions which are available to neutralize acids added to whole blood represented in milliequivalents per liter is a sensitive indication of any shifts in acid-base balance. Changes in buffer base in these patients were minimal.

TABLE III. ACID-BASE BALANCE
(8 Patients)

BEFORE PERFUSION			END OF PERFUSION			CHANGES		
pH	pCO_2	BB	pH	pCO_2	BB	pH	pCO_2	BB
7.38	43.3	44	7.46	42.7	42.8	+0.08	−0.6	−1.2

Inasmuch as these experimental and clinical observations represent actual use of the different oxygenator chamber sizes inherent in the new equipment, the indications for the use of the various sizes and the validity of a recommendation that such variations be applied are evident.

The design of the equipment to satisfy the requirement of complete removal of gas bubbles and the use of a minimum amount of antifoam has been discussed. In previously designed bubble oxygenators the contact between the blood-gas mixture and the antifoaming surface is one in which the blood runs over the portion of the equipment which has been coated with antifoam. In the present oxygenator the antifoam surface is contacted in an entirely different manner. Solid blood flows through with minimum antifoam contact while the floating bubbles rise against the treated surfaces only to the required extent. The skimming action of a series of baffles built into the defoaming chamber permits only the lower bubble-free levels of blood-oxygen mixture to pass from one part of the chamber to another, holding behind the foam to be acted upon by the treated surfaces as necessary.

A third mechanical principle is inherent in the equipment which facilitates the escape of small bubbles to the surface of the blood layer. All blood passes over the final bottom of the defoaming chamber in a thin layer. The distance to the surface in this layer is very small, and the escape of any remaining small bubbles is accomplished.

The manner in which the blood is passed from the defoaming chamber into the reservoir has been described. This prevents splashing with possible reformation of gas bubbles. Another mechanism for re-formation of gas bubbles within the presently described equipment might have developed because of the tendency for the Sigmamotor pump to produce brief return impulses or retrograde impulses of the blood as it is being pumped from reservoir to patient. It is evident that the connection between defoaming chamber and reservoir must not be airtight, but rather that vents must be provided to permit the air above the reservoir blood to be at atmospheric pressure. The locations of these vents are indicated in Fig. 1.

Another limitation of the rate of flow was considered initially to be the hemolysis which might occur as greater amounts of blood were exposed per minute to the bubbling process. In practice, hemolysis proved to be a small problem even at high flow rates. The lack of increased damage to red cells at high flow is a result of the fact that the time in the mixing chamber is the same using small or high flow because of the changes in sizes of the chambers.

The design of the reservoir incorporates certain features which deserve emphasis in relation to high flow. These concern the withdrawal of blood from

the reservoir which may become traumatic both because of velocity and negative pressure, particularly at the filters. The use in the present equipment of four vertical withdrawal outlets of comparatively large size (½ inch internal diameter) produces quiet and efficient withdrawal of blood from the reservoir. The use of four filters, one to each outlet, provides a maximum filtration area compatible with convenience. The filters used are plastic cylinders containing siliconized stainless steel wire mesh surfaces. A very large filtration area results from the use of four units. An efficient removal of any fibrin clots is accomplished, while at the same time there is a slow rate of blood flow per square area of filter. Minimum suction was produced and minimum resistance was obtained.

TABLE IV

WEIGHT (KG.)	FLOW (ML./KG./MIN.)	OXYGENATOR CHAMBER	MAXIMUM / OPTIMUM FLOW / MINIMUM	OXYGEN (L./MIN.)
0-15	90-110	I	1,300 / 400-900 / 200	3
15-31	80- 90	II	2,400 / 1,500-2,100 / 1,300	5
31-60	70- 80	III	4,200 / 2,800-3,600 / 2,400	5
60	60- 70	IV	5,600 / 4,500-5,200 / 4,200	7

SUMMARY

A bubble oxygenator has been described which incorporates certain new mechanical principles which permit use of high volumes of perfusion with stable blood chemistry, minimum trauma, and freedom from danger of the production of air embolism.

Evidence has been presented which demonstrates the requirement that the size of the chamber in which bubble oxygenation is carried out must be varied in proportion to the rate at which blood will be passed through the chamber. The sizes of the chambers incorporated in the final equipment were selected from a larger number of sizes which were tested in the experimental animal. The equipment is designed in such a way that the various oxygenator chamber sizes are obtained in an economical fashion using a minimum number of parts. Table IV incorporates the blood and oxygen flows for each oxygenator chamber.

In this equipment the removal of gas bubbles was effective at very high rates of perfusion. It is accomplished to a large extent by mechanical skimming, and minimum contact of blood with an antifoam-coated surface is required.

The oxygenator is constructed of stainless steel for ease of sterilization. It incorporates the use of heat-exchange surfaces for the maintenance or change of the temperature of the perfused blood.

The oxygenator has been tested and used in conjunction with the Sigma-motor-type pumps utilizing positive venous return through the pump head. Auxiliary charging reservoir and intracardiac suction reservoirs are incorporated in the equipment.

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CEREBRAL EMBOLISM BY ANTIFOAM A IN A BUBBLE OXYGENATOR SYSTEM:

An Experimental and Clinical Study

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IT was shown in a report from this laboratory[25] that intracarotid injection of Antifoam A causes embolic infarction in the brains of experimental animals. A method was given for anatomic demonstration of the Antifoam A emboli The question then arose of whether these emboli occurred when Antifoam A was used as recommended in a bubble oxygenator system. Cerebral Antifoam A emboli, focal destruction of neurons, and infarction of cerebral tissue in dog and man have been found after total body perfusion, and are here reported.

MATERIAL AND METHODS

Experimental.—Seven dogs of weights from 12 to 18 kilograms underwent total cardiopulmonary by-pass with a helix reservoir bubble oxygenator.[6] The debubbling chamber was coated in the usual manner[6] except in Dog 1, in which much less than the customary amount of Antifoam was used. Anesthesia was induced with intravenous thiopental sodium. A thoracotomy was performed through the right fifth intercostal space, and tapes were placed around the superior and inferior venae cavae. The external jugular vein and common carotid artery were cannulated in the neck. The venous catheter was passed through the cavae to the level of the diaphragm and the tapes were tightened to divert all blood to the oxygenator. Heparin (1.0 mg. per kilogram of body weight) was given intravenously. Perfusion time ranged from 23 to 56 minutes. Blood flow was from 25 to 80 ml. per kilogram per minute. The catheters were withdrawn at the end of the perfusion, and protamine was given intravenously to return the clotting time to normal. The wounds were closed in layers with silk sutures and the right pleural cavity was drained with water-sealed suction for 3 to 5 hours postoperatively.

Penicillin and streptomycin were given for 3 days postoperatively. The animals were observed carefully during the postoperative period for signs of neurologic deficit and were sacrificed from 7 to 50 days postoperatively by means of pentobarbital anesthesia. The thoracic aorta was bisected and the brain was removed promptly and suspended in a solution of 10 per cent formalin in isotonic saline. After hardening, the brains were cut in the coronal plane and examined

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macroscopically. Representative blocks of whole coronal sections were embedded in celloidin, cut at 20 μ, and stained by the techniques of Nissl and Weil. Additional blocks were frozen and sectioned at 15 μ and facing sections were stained with oil red O and osmic acid.[25]

Clinical.—Five patients, ranging in age from 7 months to 43 years, underwent open cardiotomy and total cardiopulmonary bypass with a DeWall III bubble oxygenator. These patients were selected from a large group who had undergone open heart operations with the bubble oxygenator. The majority of patients had successful outcomes. Only the fatalities are included in this study.

The heart was exposed with a median sternotomy and then an exploratory right atriotomy was performed. Venous catheters were inserted through the right auricular appendage into each vena cava, and an arterial catheter was inserted into the femoral artery. The patients received heparin (1.5 mg. per kilogram of body weight) before the catheters were placed. Blood flow ranged from 40 to 85 ml. per kilogram per minute. After the bypass and removal of catheters, protamine was given intravenously to return the clotting time to normal.

Brief abstracts of the case records of each patient are given. Representative blocks were taken for paraffin and celloidin embedding and for frozen sections as in the animal experiments.

CASE REPORTS

CASE 1.—V. B., a 33-year-old woman, was admitted to the North Carolina Baptist Hospital for correction of a ventricular septal defect diagnosed 1 year previously. The patient had exertional dyspnea, occasional ankle edema, and acrocyanosis after exercise. Pulmonary artery pressure was 109/48.

At operation, the pulmonary artery was approximately 2½ times the diameter of the aorta, and the right ventricle greatly enlarged. A ventricular septal defect in the membranous portion of the septum was approximately 2.5 cm. in diameter. Cardiopulmonary bypass at a flow rate of approximately 50 ml. per kilogram per minute was maintained for 36 minutes and the defect was directly sutured. After restoration of cardiac activity, arterial blood did not appear well oxygenated. Bradycardia and a drop in systemic arterial pressure were then noted. The myocardium did not respond either to electrical stimulation with a pacemaker, or to various drugs.

Postmortem examination revealed moderate cardiac hypertrophy. The heart weighed 370 Gm. and there were 2 ventricular defects. The upper defect was 2.5 cm. in diameter and was repaired. The lower defect was a slit with probe patency. In addition, a 1.2 cm. atrial defect was noted. All lobes of the lung were moderately atelectatic, and the pulmonary vessels were severely arteriosclerotic. The brain was macroscopically normal, but the capillaries were distended and many contained emboli stained with red O. A single capillary was found with material reacting with osmic acid. This indicated a single fat embolus.

Comment: This was the only case of fat embolus in the series, although Antifoam A was the predominant embolic material. Death resulted from cardiac standstill.

CASE 2.—M. N., a 7-month-old boy, had a history of frequent colds and "sniffles" since birth, and pneumonia 3 weeks prior to admission. The child gained weight poorly and weighed only 8 pounds, 15 ounces when admitted to the hospital. Studies led to the tentative diagnosis of a large left-to-right intracardiac shunt, most probably a ventricular septal defect. A decision was made to delay operative repair for at least 1 to 2 years if possible. While in the hospital, the child developed cardiac failure refractory to medical treatment and operation was recommended only in a desperate effort to save his life.

Cardiopulmonary bypass was created at flow rates of 70 to 85 ml. per kilogram per minute. Cardiac arrest was induced with potassium citrate. Through a right ventriculostomy, a large membranous ventricular septal defect was found which was repaired with interrupted silk sutures. A patent foramen ovale was also found and was repaired through the tricuspid valve. The bypass was terminated successfully but ventricular rhythm was idiopathic and indicative of heart block. Braided wire alloy was therefore inserted into the myocardium of the right ventricle and the heart was restored to normal rhythm with the pacemaker. The patient was returned to the recovery room in apparently good condition but developed ventricular fibrillation 35 minutes afterward and did not respond to resuscitative measures including massage and electroshock.

Postmortem examination revealed a heart of 80 Gm. (expected normal weight 37 Gm.) with repaired atrial and ventricular septal defects, and severe atelectasis and hemorrhage in both lower lobes of the lung. The brain was grossly normal. On microscopic examination, the capillaries generally were distended, and a moderate number of arterioles and capillaries contained emboli stained with oil red O. The neurons were normal in appearance.

Comment: Too little time elapsed after cardiotomy to permit development of significant changes in the cerebrum, but Antifoam A emboli were present.

CASE 3.—M. A. K., a 6-year-old girl, was admitted to the hospital for repair of a previously diagnosed high interventricular septal defect with pulmonary hypertension (71/38). She had poor exercise tolerance, cyanosis with exercise, and frequent "chest colds" with pneumonia.

Cardiopulmonary bypass was established at a flow rate of 70 ml. per kilogram per minute. Cardiac action was arrested with potassium citrate, and a large ventricular septal defect was closed with a polyvinyl sponge. The 46 minute period of cardiac bypass was well tolerated, and an effective cardiac systole with a regular rhythm occurred afterward. The patient was doing well when the heart suddenly stopped 3 hours after cardiotomy. None of the usual resuscitative measures were effective.

At necropsy the heart weighed 200 Gm. (expected normal weight 95 Gm.) and contained the repaired 3.5 cm. septal defect. The lungs were moderately atelectatic. A lipoma of the corpus callosum and agenesis of the corpus callosum and inferior vermis of the cerebellum were present, but the brain was otherwise normal in gross appearance. Details of the congenital cerebral anomalies have been published separately.[29] Microscopic examination of the brain revealed capillary engorgement and occlusion of many vessels by emboli stained with oil red O. The neurons were structurally intact in Nissl stains.

Comment: The congenital anomalies of the brain were incidental findings. The immediate cause of death was cardiac arrest. Antifoam A emboli were present, but insufficient time had elapsed to allow determination of the extent of cerebral damage.

CASE 4.—S. J. G., an 8-year-old girl, was admitted to the hospital for elective repair of a previously diagnosed pulmonary outflow tract obstruction. Easy fatigability, limitation of activity, lack of weight gain, cyanosis with exercise, and cardiomegaly led to the recommendation of repair.

The patient underwent total cardiopulmonary bypass, and cardiac arrest was induced with potassium citrate. A fibromuscular type of infundibular stenosis with a striking third chamber effect was found and the stenotic ring was excised. The bypass lasted 21 minutes with a flow rate of 70 ml. per kilogram per minute. The procedure was well tolerated and the patient was in good condition during the immediate postoperative period except for mild restlessness. She continued to do well for 8 hours after cardiotomy, but then suddenly gasped for breath and stopped breathing. Attempts at resuscitation were unsuccessful.

Permission for postmortem examination was limited to the thorax and head. The heart weighed 150 grams, and the muscular band in the right ventricle had been completely resected. A ventricular septal defect was not present. The brain was macroscopically normal. Routine paraffin sections were unremarkable. Larger blocks embedded in celloidin revealed

foci of extravasation of red blood cells from capillaries, and small zones of destroyed neurons. Antifoam A emboli were seen in capillaries in these altered regions. The small blood vessels generally were dilated and distended.

Comment: There was little anatomic evidence of the cause of death, probably because of the short time elapsing between cardiotomy and death. The changes in the brain were minimal but definite, and indicated that Antifoam emboli contributed to an interference with cerebral circulation.

CASE 5.—J. P. P., a 43-year-old man, was admitted to the hospital for treatment of a known atrial septal defect. Indications for surgery included increasing exertional dyspnea and cardiomegaly. Pressure in the pulmonary artery was normal.

Exploratory atriotomy revealed an atrioventricularis communis type of atrial septal defect with a cleft in the mitral valve. The patient underwent cardiopulmonary bypass for 30 minutes without cardiac arrest at a flow rate of 40 to 50 ml. per kilogram per minute. A polyvinyl sponge was placed in the defect and the mitral valve was sutured. The patient was slow to recover from anesthesia but was responding to command and apparently improving on the second postoperative day when severe bronchospasm developed. A tracheostomy was performed and large doses of aminophylline, isoproterenol, and hydrocortisone were used with only moderate success in effecting good respiratory exchange. On one occasion deep ether anesthesia was required to relax bronchospasm. The patient's condition grew steadily worse in spite of added support from respirators and vasopressors. Death occurred on the fourth postoperative day.

The general necropsy revealed severe pulmonary edema and atelectasis. The heart weighed 530 Gm. and contained the repaired septal defect. The brain was externally normal, but the surface of each section contained numerous petechiae in gray and white matter. The hemorrhages were only a few millimeters in greatest diameter, but were present in cerebrum, cerebellum, and brain stem. Microscopic sections revealed many small hemorrhagic and ischemic infarcts. Capillaries within these small infarcts were often occluded by Antifoam seen in oil red O preparations.

Comment: This patient survived the longest time of any in this series, and had the greatest amount of demonstrable cerebral damage. Bronchospasm and resulting pulmonary edema undoubtedly played a role in the death of this patient. Hypoxia, as a consequence of impaired cardiopulmonary function, and increased venous pressure could have contributed to the hemorrhagic component of the cerebral lesions.

RESULTS

The findings in the animals are summarized in Table I. There were no deaths or apparent morbidity. The dogs tolerated the perfusion without significant change of the vital signs. They recovered rapidly from anesthesia, were then alert, and ate well. There was no evidence of neurologic or other abnormalities. The brains were normal on macroscopic examination. Microscopic study, however, revealed scattered foci of loss of neurons, and microinfarcts in every section. These lesions ranged from 50 μ to 4 mm. in greatest dimension. A representative minimal alteration is illustrated in Fig. 1, characterized by an absence of neurons, and creating a pale zone. Typical larger and older lesions are illustrated in Fig. 2.

Antifoam A stained by oil red O was found scattered diffusely in the capillaries of gray and white matter. These emboli differed greatly in size and configuration. Some were homogenous plugs, but others were aggregates of tiny particles. The emboli were generally smaller in the animals with longest survival after perfusion, and many emboli did not completely fill the lumens of the

Fig. 1.

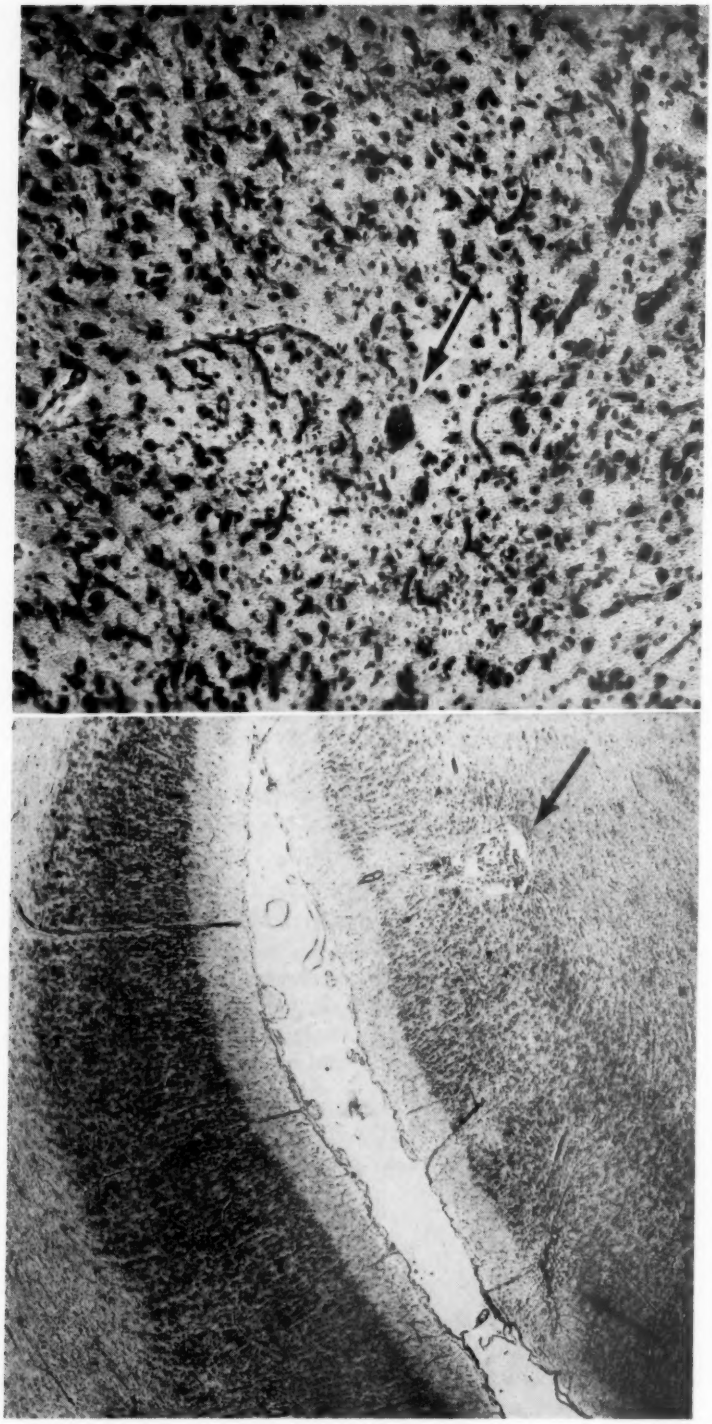

Fig. 2.

Fig. 1.—(Dog 2.) Photomicrograph of cerebral cortex. Neurons have irregularly disappeared in the zone around the distended capillary shown by the arrow. The glial stroma is intact, and a few other capillaries are visible. (Nissl's technique; ×125.)

Fig. 2.—(Dog 3.) Photomicrograph of cerebral cortex. Neurons and stroma are destroyed in these microinfarcts. The upper arrow designates a liquefied zone, the lower arrow a zone of coagulative necrosis. The cortex is normal on the other side of the sulcus. (Nissl's technique; ×25.)

capillaries. The emboli were larger, however, in the animals sacrificed within 2 weeks after perfusion.

The findings in the 5 patients are summarized in Table II. Capillaries distended with erthrocytes were seen in foci of 0.2 mm. to 4.0 mm. diameter, predominantly in the cortex, in patients who died in 1 to 3 hours. Many neurons in these foci were chromatolytic or pyknotic. When survival time was longer, erythrocytes leaked from blood vessels to create pericapillary hemorrhages. In addition, neurons were destroyed in small foci characterized by poor staining of the internuclear substance, and pyknosis and loss of neurons. When survival time extended to a few days, anemic (and in 1 case hemorrhagic) infarcts were created (Fig. 3), and finally necrosis of interstitial tissue occurred.

TABLE I

DOG NO.	PUMP TIME (MIN.)	BLOOD FLOW (ML./KG./MIN.)	DURATION OF LIFE (DAYS AFTER PERFUSION)	MICROSCOPIC FINDINGS IN BRAIN			SPECIAL STAINS	
				FOCAL LOSS OF NEURONS	TISSUE NECROSIS	CAPILLARY DAMAGE	OIL RED O	OSMIC ACID
1	45	50	7	+	–	–	+	–
2	35	32	12	+	+	–	++	–
3	56	60	31	+	++	+	++	–
4	30	45	33	+	++	+	++	–
5	25	40	42	+	++	+	++	–
6	25	50	43	+	++	+	++	–
7	23	40	50	+	+++	+	++	–

Antifoam A emboli (stained with oil red O occluded many capillaries and were scattered diffusely, but predominantly in the cortex (Fig. 4). The facing sections stained with osmic acid were negative except for a single capillary embolus (Case 4).

DISCUSSION

Cerebral emboli were a major complication in the early experimental studies of extracorporeal circulation with a bubble oxygenator system. Helmsworth and associates[17] found characteristic signs of cerebral damage in the dying animals, but a systematic study of the brains was not made. Clowes and associates[3] reported 34 deaths in 74 experiments and concluded that air and fibrin emboli were the major causes of death. In the early experiments of Newman and associates,[22] there were only 20 survivors of 62 perfusions, and they concluded that air embolism was a major problem. Although there were many technical problems and involvement of other parts of the body secondary to perfusion,[1, 2, 4, 5, 7, 15, 19] the obvious damage to the central nervous system was alarming.

The numerous experimental studies attest to the difficulties in defining the cause of cerebral damage. Air, fibrin, and Antifoam A were considered probable sources of emboli in the bubble oxygenator system. Some investigators[2, 17] found small bubbles in the blood pumped into the arteries of the animals. Others[11, 21] used special techniques to show air in the cerebral vessels after perfusion. Furthermore, any doubt of the destructive effects of intra-arterial gas emboli

TABLE II

	AGE (YEARS)	DEFECT	PUMP TIME (MIN.)	BLOOD FLOW (ML./KG./MIN.)	DURATION OF LIFE (HOURS AFTER PERFUSION)	POST-OPERATIVE STATUS	MACROSCOPIC FINDINGS IN BRAIN	MICROSCOPIC FINDINGS IN BRAIN			SPECIAL STAINS	
								CAPILLARY DISTENTION	PERICAPILLARY HEMORRHAGE	FOCAL NEURONAL DESTRUCTION	OIL RED O	OSMIC ACID
1	33	Ventricular septal defects	36	50	1	Died in operating room	Normal	+	–	–	+	±
2	7/12	Ventricular and atrial septal defects	60	70-85	3	Did not recover after anesthesia	Normal	+	–	–	+	–
3	6	Large ventricular septal defect. Severe pulmonary hypertension	46	70	3	Did not recover after anesthesia	Normal*	+	–	–	+	–
4	8	Congenital infundibular pulmonic stenosis	21	70	8	Normal	Normal	+	+	+	+	–
5	43	Atrial septal defect	30	40-50	96	Slow recovery from anesthesia	Multiple petechiae	+	+++	+++	+	–

*Except for congenital defects in cerebellum and corpus callosum.

Fig. 3.

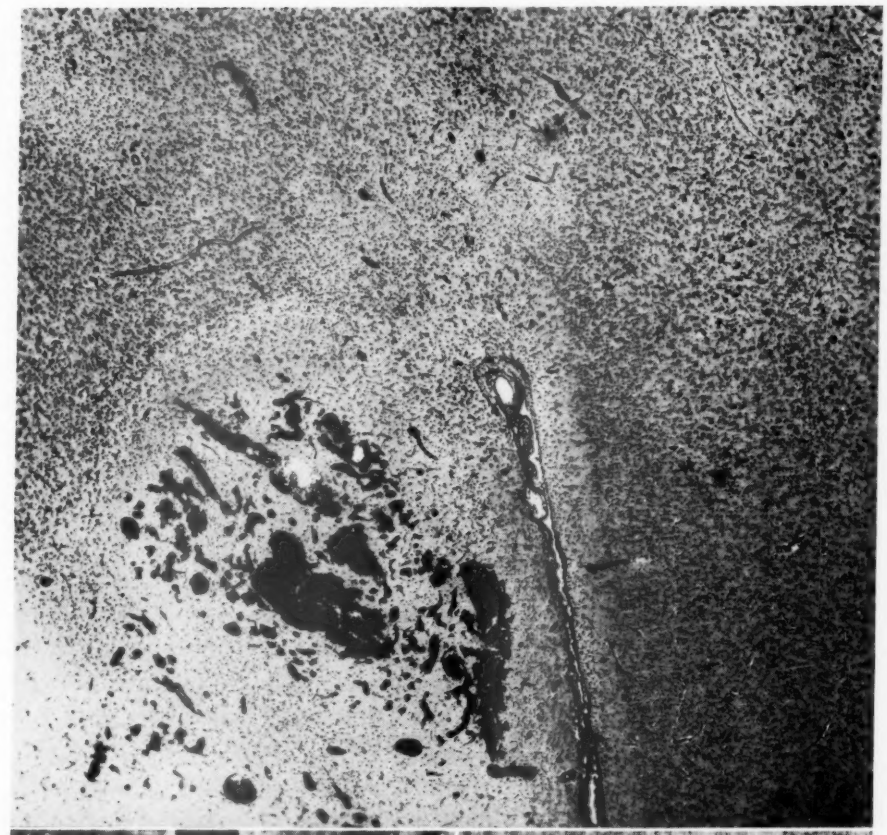

Fig. 4.

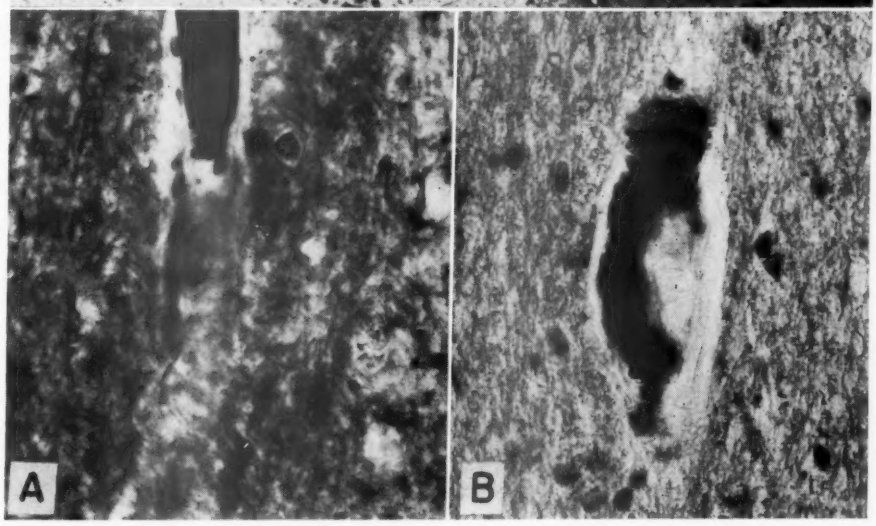

Fig. 3.—(Case 5.) Photomicrograph of cerebral cortex. The architecture is normal on the reader's right. A large ischemic infarct is present on the left. The dark masses are the central hemorrhagic portion. (Nissl's technique; ×25.)

Fig. 4.—Photomicrographs of emboli in cerebral blood vessels. *A*, (Case 1.) Complete occlusion of vessel by Antifoam A. *B*, (Case 4.) Incomplete occlusion by less concentrated material. (Oil red O technique; ×440.)

was dispelled by experimental studies[5, 6] which showed severe damage to the brain after injection of small quantities of air into the cerebral arteries of dogs.

Antifoam A was considered innocuous[17, 27] until Giannelli and associates[11] demonstrated particles of this substance in the perfused blood and showed some correlation between amount of brain damage and quantity of Antifoam used. Subsequently, damage to the "blood-brain barrier" was studied by a technique employing fluorescein; and again the quantity of Antifoam was correlated with the amount of damage to the "blood-brain barrier."[16] DeWall and associates[6] conceded that Antifoam, if used in excess, could be swept into the arteries as emboli. Finally, cerebral embolism by Antifoam A was demonstrated conclusively in a report from this laboratory.[25] Antifoam A emboli and microinfarcts were found in the brain after injection of Antifoam into the internal carotid artery of dogs. The oillike properties of Antifoam and the resemblance of the pathologic findings to those in cerebral fat embolism were discussed. Reed and Kittle[26] also demonstrated pathologic changes in dogs after intravenous and intra-arterial injection of Antifoam A. Nevertheless, cerebral emboli of Antifoam, when the defoaming agent was used correctly in the bubble oxygenator, were not demonstrated.

Some of the studies cited led to improvements in the bubble oxygenator. Reservoirs[11, 23] and filters[12] were added. The blood was returned to the femoral rather than the subclavian artery. It was suggested that only a small amount of Antifoam be used. Consequently, the problem of mortality and morbidity related to neurologic damage appeared to be overcome. Recent data[6, 10, 18, 24] indicate that open heart surgery with a heart-lung machine has become a conventional surgical procedure, and suggest that extracorporeal circulation in itself does not adversely affect the patient.

The demonstration of Antifoam emboli in this study of the brain of dog and man after total cardiopulmonary bypass with a bubble oxygenator system not only confirms the impressions of other investigators that Antifoam A may enter the blood stream as emboli or alter the "blood-brain barrier," but also confirms that it occludes cerebral capillaries and damages cerebral tissue. Furthermore, it is not necessary to have excess of Antifoam to form emboli. Far less than the usual amount[18] of Antifoam was used in the defoaming chamber for Dog 1 and emboli were present, although few in quantity. Reducing the volume of Antifoam merely decreased the number of emboli. Therefore, an excess of Antifoam can result in obvious signs of damage to the central nervous system, but a small amount may not produce overt neurologic signs or morbidity. The smaller volume of Antifoam decreases the extent of neuronal destruction below the threshold of clinical and macroscopic observation.

It has been emphasized that Antifoam is effective in extremely small quantities. The effectiveness, however, is expressed in parts per million and implies adequate dispersion. If the Antifoam remained on the chamber wall, it would be less effective. Antifoam is consumed in the defoaming process. It is also consumed in the defoaming chamber of the bubble oxygenator. If the perfusion is prolonged, the defoaming chamber may become ineffective and must be replaced by another chamber coated with Antifoam.[6] Therefore, it is

difficult to conceive how Antifoam can defoam blood effectively without becoming suspended in the blood entering the patient.

The parenchymal lesions observed in the animal brains are identical with those found after the injection of Antifoam into the internal carotid artery.[25] Two patients in this series survived long enough to develop characteristic lesions. Nevertheless, it should be emphasized that the animals were "normal," and the human beings had no obvious neurologic signs. Moreover, the brains were almost always macroscopically "normal." Therefore, the excellent clinical results obtained by some workers with the bubble oxygenator are not surprising. What is the effect of the widespread, focal destruction of small numbers of neurons? It would most certainly depend on the quantity and location of neurons destroyed. Higher cerebral functions would be affected first and the effects probably could be detected earliest by psychometric studies.

The data presented in Tables I and II allow accurate determination of the times necessary for histologic demonstration of damage to cerebral tissue. Undoubtedly, physiologic alterations occur earlier.

It should be recognized that these studies deal only with one part of the problem of emboli associated with extracorporeal circulation. The roles of air and fibrin emboli have not been investigated in this study, but Antifoam A embolism has been demonstrated after use of a bubble oxygenator system, and it is shown that these emboli are associated with damage to cerebral tissue.

CONCLUSIONS

1. Antifoam A embolism is a complication of cardiopulmonary by-pass with a bubble oxygenator system in which this substance is used as a defoaming agent.

2. Antifoam A embolism causes widespread focal occlusion of capillaries and may result in widespread focal destruction of neurons. These phenomena may not be apparent by macroscopic examination. There is a wide quantitative variation in both processes. The capillary occlusion is in part reversible.

3. When the bubble oxygenator is properly used, the effect of Antifoam A embolism may not be apparent in the function of animals or man by the techniques ordinarily available, but damage to the brain may be revealed by microscopic examination.

4. More than 3 hours, but less than 8 hours, must elapse after occlusion of blood vessels in human beings to allow demonstration of neuron damage by the technique of Nissl. Neurons are destroyed first, and supportive tissue later. Capillaries promptly distend, but leakage of red blood cells occurs in association with destruction of neurons.

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HEMODYNAMIC OBSERVATIONS IN EXPERIMENTAL MITRAL REGURGITATION

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THE modifications of the left atrial pulse pressure contour which result from experimentally produced mitral regurgitation have been well characterized.[4, 5, 8] In addition, a method for the quantification of regurgitation from the left ventricle to the left atrium by means of a metered left ventriculoatrial shunt has been described.[2] This latter technique was modified so that in an inelastic regurgitant system containing an electromagnetic flowmeter, a quantitative study could be made of some of the phasic pressure-flow relationships between the left ventricle and the left atrium. The effects of several pharmacologic agents on the left atrial pulse contour were also investigated both in dogs with ventriculoatrial regurgitation and in others with chronic mitral regurgitation produced by operation. The results of these studies are described in the present report.

METHODS

The experiments were carried out in 15 mongrel dogs weighing from 12 to 24 kilograms. Thiopental sodium anesthesia was employed and ventilation was maintained, after tracheal intubation, with a demand respirator.

In 5 dogs a left thoracotomy was performed and a left ventriculoatrial shunt constructed by a modification of the technique described by Braunwald and associates.[2] Following the administration of heparin, 2 mg. per kilogram, a curved metal cannula with an internal diameter of 9 mm. was inserted through the apex of the left ventricle. The cannula was connected by metal tubing, through one flowmeter, to the left atrial appendage (Fig. 1). In some experiments a short, thick-walled segment of plastic tubing was inserted into the apicoatrial shunt circuit, permitting the regulation of regurgitant flow by constriction of the shunt with a screw clamp. The lack of compliance in the apicoatrial shunt circuit and the negligible resistance of the electromagnetic flowmeter cannula resulted in minimal distortion of the left atrial pressure responses to the regurgitant volume.

The flowmeters employed were the electromagnetic type described by Richardson,[7] and provided high speed recordings of pulsatile blood flow. The flowmeter tracings were inscribed with a time lag of approximately 0.02 second; this delay resulted from the resistance-capacitance coupling in the output circuit of the flowmeter amplifier which was necessary to provide ripple-free recordings. Pressure-flow-time relationships were corrected by this factor in all data subsequently presented.

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Effective systemic blood flow was measured by means of a second electromagnetic flowmeter in the descending thoracic aorta. The vessels arising from the aortic arch were ligated and cerebral blood flow was supplied by means of a shunt from the femoral artery to the distal end of the brachiocephalic artery (Fig. 1). Pressures were measured in the aortic arch, left ventricle, and left atrium through plastic catheters attached to Statham P-23-D pressure transducers and were recorded together with pulsatile and mean flows on a multichannel direct-writing oscillograph. The frequency response of the catheter strain gauge recording system employed was uniform to approximately 30 C.P.S.[3] High-speed recordings were made during the preregurgitation control period, and again 3 to 5 minutes after regurgitation had been induced and when pressures and flows had stabilized. Total blood volume was increased by transfusion of whole blood during some experiments.

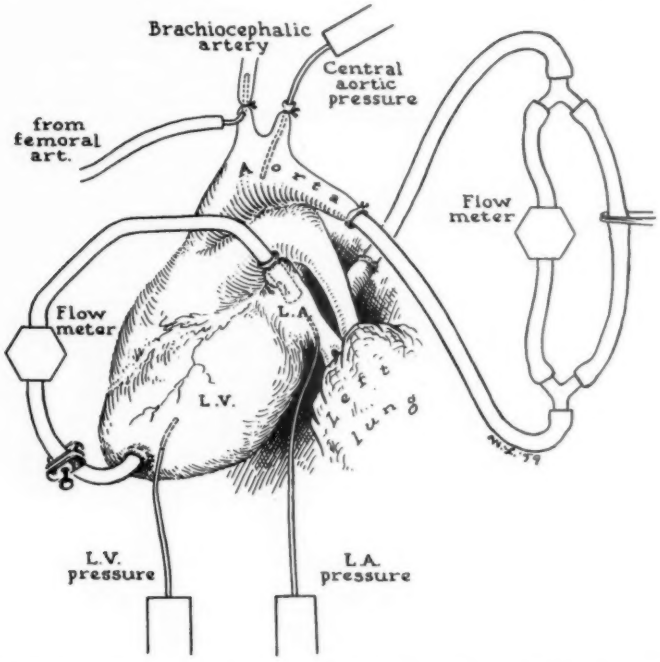

Fig. 1.—Schematic representation of the apicoatrial shunt and monitoring systems employed.

In 7 dogs, mitral regurgitation was produced 3 to 6 months prior to study by the technique described by Haller and Morrow.[4] In these animals a left thoracotomy was performed and pressures were measured in the aorta and left atrium during the infusion of various drugs. In 3 additional dogs with normal mitral valves pressures were also measured in the left atrium and aorta during the infusion of these same agents. Norepinephrine was administered intravenously in a concentration of 0.009 mg. per cubic centimeter at a rate of 20 to 30 drops per minute. Methoxamine was given in a single intravenous injection of 0.01 mg. per kilogram. Single intravenous doses of 0.25 mg. of neostigmine were administered sequentially until significant cardiac slowing was obtained.

RESULTS

The Effects of Mitral Regurgitation on the Left Atrial Pressure and Pulse Contour.—Data obtained during the production of metered ventriculoatrial regurgitation in 5 dogs are summarized in Table I. Pressure and flow tracings

TABLE I. HEMODYNAMIC EFFECTS OF METERED MITRAL REGURGITATION

DOG NUMBER	TIME	HEART RATE	MEAN PRESSURES (MM. HG)		LEFT ATRIAL (V WAVE MM. HG)	MEAN FLOWS (ML./MIN.)	
			AORTA	LEFT ATRIUM		SYSTEMIC	REGURGITANT
1	Control	126	80	11	16	995	
	Initial regurgitation	132	60	16	22	700	2,730
	Stabilized regurgitation	120	90	18	32	955	3,885
2	Control	158	131	3	4	1,490	
	Initial regurgitation	135	108	6	14	1,140	
	Stabilized regurgitation	135	117	7	10	1,250	3,090
3	Control	104	67	6	8	1,410	
	Initial regurgitation	103	52	8	14	1,380	2,010
	Stabilized regurgitation	104	55	8	15	1,320	1,920
4	Control	144	160	11	11	1,230	
	Initial regurgitation	142	149	12	17	1,130	2,400
	Stabilized regurgitation	148	165	13	17	1,220	2,300
5	Control	122	150	4	5	1,340	
	Initial regurgitation	126	133	9	13	1,300	2,460
	Stabilized regurgitation	136	136	10	18	1,340	2,850

recorded during one of these experiments are reproduced in Fig. 2. When the shunt was fully open regurgitant flow averaged 2,830 ml. per minute and ranged from 1.9 to 4.1 times effective systemic flow (Table I). During the initial 10 to 12 cardiac cycles following the onset of regurgitation, a decrease in aortic pressure averaging 15 mm. Hg was observed (Fig. 2). Simultaneous reductions in effective systemic blood flow ranging from 2 to 26 per cent and averaging 13 per cent also occurred. Subsequently, both pressure and systemic flow gradually returned toward control level in each experiment. Mean left atrial pressures averaged 4 mm. Hg higher than control values, the increases ranging from 2 to 7 mm. Hg. The average increase in the height of the v wave was 10 mm. Hg; the increases ranged from 6 to 16 mm. Hg. In all experiments the peak of the v wave occurred after maximum regurgitant flow. The average time difference between the v wave peak and the time of maximum regurgitant flow rate was 0.14 second. Although the maximum rate of regurgitation occurred during mid-injection, regurgitant flow at a diminished rate continued into relaxation in all experiments.[8]

The effects of variations in regurgitant flow on the height of the left atrial v wave in 2 dogs are presented graphically in Fig. 3. Regurgitant flows equal to or exceeding effective forward output were required to evoke a two-fold increase in v wave height. Although large amounts of regurgitation were necessary to produce striking alterations in peak v wave pressure, other changes

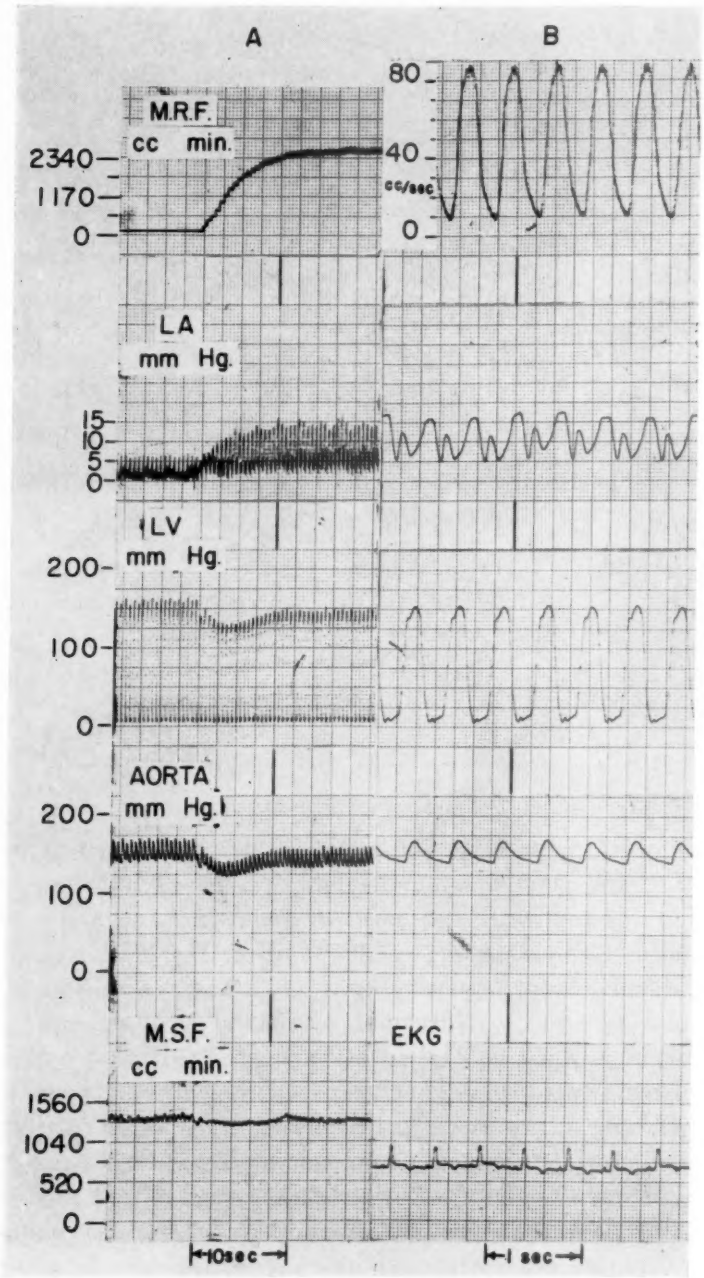

Fig. 2.—Simultaneous recordings of mean regurgitant flow *(M.R.F.)*, left atrial *(L.A.)*, left ventricular *(L.V.)*, aortic pressures and mean systemic flow *(M.S.F.)*. *A* was recorded at the onset of regurgitation and *B* following stabilization. In *B* phasic regurgitant flow was recorded.

in the left atrial pulse contour were noted with smaller degrees of regurgitation. As shown in Fig. 4, the most pronounced changes occurred during the first 0.10 to 0.15 second following the onset of ventricular contraction and were characterized by an abbreviated x descent, and an early onset of the v wave ascent.

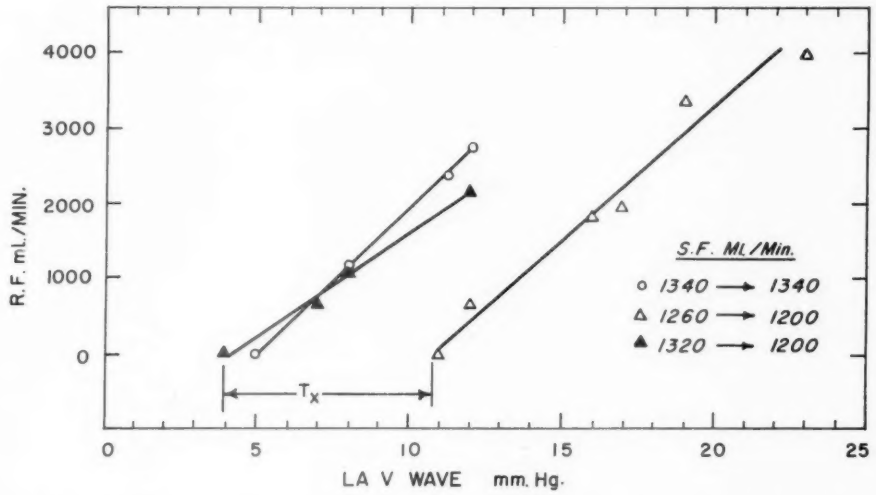

Fig. 3.—Graphic representation of the relationship between variations in regurgitant flow and the height of the left atrial v wave. Systemic flows *(S.F.)* for each experiment are shown. The flow-pressure relationships following transfusion of whole blood *(Tx.)* are shown by open triangles.

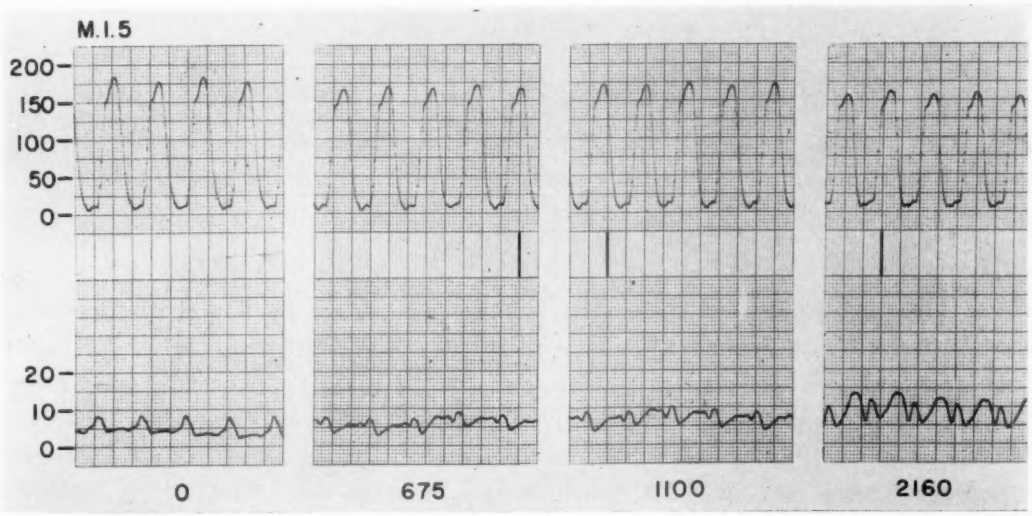

Fig. 4.—Simultaneous left ventricular *(upper tracings)* and left atrial *(lower tracings)* pressures recorded as regurgitant flow were progressively increased. The quantity of regurgitant flow (milliliters per minute) is shown beneath the appropriate panel.

Following the infusion of whole blood the same range of regurgitant flows was associated with higher v wave peaks (Fig. 3). Prior to transfusion the v wave excursion (the difference between v wave height and the lowest point in the y descent) during maximum regurgitant flow was 4.5 mm. Hg and mean

left atrial pressure was 5 mm. Hg. With the same regurgitant flow the excursion measured 5.5 mm. Hg following transfusion, and the mean left atrial pressure increased to 15 mm. Hg. With further increases in the quantity of regurgitation in the transfused dog, however, the v wave excursion progressively increased to 12 mm. Hg. The time interval between peak v wave pressure and peak rate of regurgitant flow following transfusion measured 0.10 second, compared with 0.16 second during maximum regurgitation prior to transfusion.

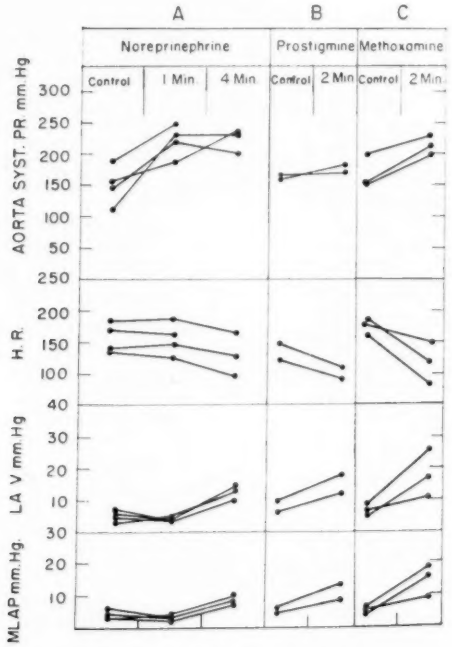

Fig. 5.—Graphic representation of the alterations in aortic systolic pressure, heart rate *(H.R.)*, height of the left atrial v wave *(LA V)*, and mean left atrial pressure *(MLAP)* induced by norepinephrine, neostigmine, and methoxamine.

Effects of Pharmacologic Agents on Regurgitant Flow and the Left Atrial Pressure Pulse Contour.—

Norepinephrine infusion: In 4 dogs with chronic mitral regurgitation administration of norepinephrine resulted in an initial fall in mean left atrial pressure, and a decrease in v wave height (Fig. 5, *A*). During this phase, which lasted approximately 1 minute, ejection time was shortened by 0.01 to 0.03 second, while the heart rate remained relatively constant. With continued norepinephrine infusion bradycardia supervened and mean left atrial pressures and v wave heights increased (Fig. 5, *A*).

A tracing obtained during norepinephrine infusion in a dog with an apicoatrial shunt is reproduced in Fig. 6. The effect on left atrial pressure and heart rate was similar to that which occurs in dogs with chronic mitral regurgitation. The initial decrease in left atrial pressure was accompanied by diminished regurgitant flow and increased effective systemic flow and arterial pressure. With continued drug infusion left atrial pressure and regurgitation increased the heart rate decreased, and effective systemic flow was diminished.

Injection of neostigmine: Administration of neostigmine (Fig. 5, *B*) resulted in bradycardia, increased ejection time, and a minimal increase in aortic systolic pressure. Increases in left atrial v wave height comparable to

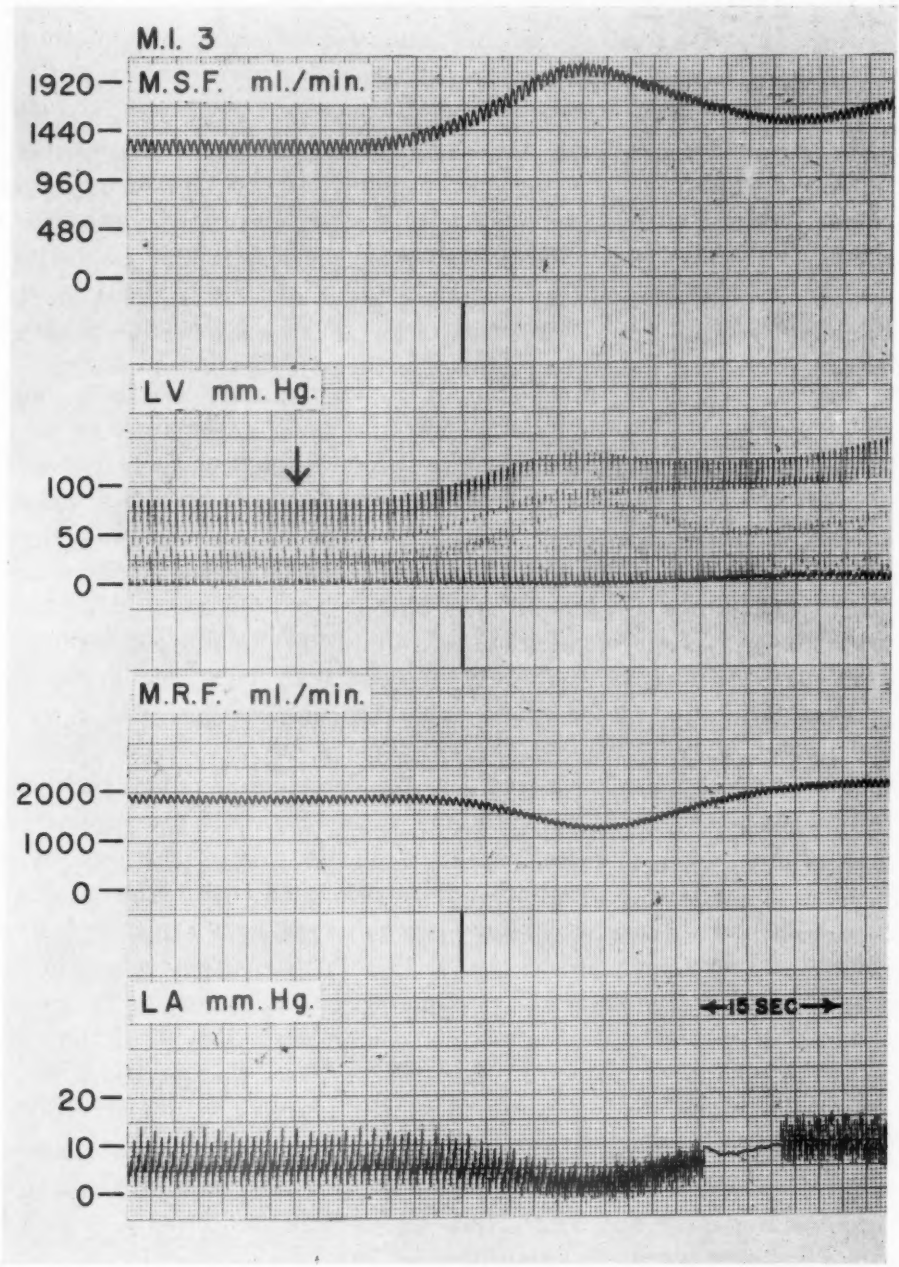

Fig. 6.—Simultaneous recordings of mean systemic flow *(M.S.F.)*, left ventricular pressure *(L.V.)*, mean regurgitant flow *(M.R.F.)*, and left atrial pressure *(L.A.)*. Norepinephrine infusion was begun at the time indicated by the arrow.

those obtained with norepinephrine infusion were observed. When neostigmine was administered after bradycardia had occurred during norepinephrine infusion, further slowing ensued and additional increases in left atrial v wave height were noted.

Injection of methoxamine: In 4 dogs with chronic mitral regurgitation methoxamine produced an immediate elevation of aortic pressure, bradycardia, and heightened v waves (Fig. 5, *C*). Ejection time was lengthened in proportion to the increase in cycle length imposed by bradycardia. An initial decrease in left atrial pressure was not observed following administration of methoxamine. In general the increases in mean left atrial pressure and v wave height were greater than those observed during norepinephrine infusion.

Similar effects on left atrial and aortic pressures were noted in dogs with apicoatrial regurgitation following methoxamine administration. A decrease in effective forward output accompanied the arterial pressor response, while regurgitant flow and v wave height increased.

Control experiments: Drug infusions were also carried out in 3 dogs without mitral regurgitation. Administration of norepinephrine, neostigmine, and methoxamine resulted in no significant alteration in v wave height.

DISCUSSION

The studies described emphasize some of the problems associated with the evaluation of mitral regurgitation in patients by analysis of the left atrial pressure pulse contour. Large ventriculoatrial flows resulted in only slight increases in mean left atrial pressure.[2] The elevations in peak v wave pressure with large regurgitant flows were somewhat more prominent than the mean pressure changes. However, pronounced alterations in other portions of the left atrial pressure pulse contour were observed with much smaller regurgitant flows. These alterations were characterized by abbreviation of the x descent and early onset of the ascent of the v wave. Thus, detailed analysis of the ascent of the v wave may prove useful in the detection of mitral regurgitation, especially when peak v wave pressure and mean left atrial pressure are within "normal" limits. When mean left atrial pressure was increased by transfusion, small amounts of regurgitation were associated with higher peak v wave pressures. The excursion of the v wave was not appreciably increased, however, until mean left atrial pressure exceeded 15 mm. Hg. These observations are compatible with the studies of the pressure-volume relationships in the excised left atria of dogs which demonstrated a change in the slope of the pressure-volume curve at approximately 15 mm. Hg.[6] Above this point on the curve, the same volume increments resulted in larger increases in left atrial pressure.

In all instances in which phasic ventriculoatrial flow was metered, the maximum rate of regurgitation occurred before the peak v wave pressure. This interval was narrowed with atrial engorgement, reflecting a change in the left atrial pressure-volume relationship.

In the presence of an essentially normal myocardium and when mean left atrial pressure is low, the flat portion of the left arterial pressure-volume curve obtains. Under these circumstances v wave height need not be elevated even when regurgitant flow approaches forward cardiac output. Similarly, a strikingly elevated v wave associated with low mean left atrial pressure implies a large regurgitant flow. It would appear that when the myocardium fails and the

mean left atrial pressure rises, an estimation of the severity of regurgitation by analysis of the left atrial pressure pulse contour is uncertain unless the left atrial pressure-volume curve can be determined.

Although the size of the orifice and pressure relationships are primary determinants of regurgitant flow, additional factors would seem to be implicated in the maintenance of forward cardiac output in the face of a large regurgitant orifice. Both the inertia of forward-flowing blood[8] and the geometry of ventricular contraction probably have important effects on the partition of total stroke volume.

Increased mitral regurgitation as a result of aortic hypertension induced by constriction of the aorta has been described,[8] and drug-induced hypertension has recently been applied as a clinical method for the detection of mild degrees of mitral regurgitation.[1] It was of interest, therefore, that diminished regurgitation accompanied shortened ejection during the initial phase of norepinephrine infusion. This occurred despite an increase in arterial pressure. Thus, the effects of aortic hypertension alone were offset by the positive inotropic action of norepinephriine, and only when ejection was lengthened by subsequent bradycardia did increased regurgitation become apparent. These effects and the studies with methoxamine and neostigmine suggest that the use of agents producing hypertension without increased myocardial contractility, or those causing bradycardia alone would provide a more sensitive clinical test for the presence of mitral regurgitation.

SUMMARY

A method is described for the study of phasic pressure-flow relationships during experimental mitral regurgitation. Alterations in the contour of the left atrial v wave occurred when changes in v wave height were not apparent. The height and timing of the v wave were dependent less upon the magnitude of regurgitation than on the degree of left atrial distention and the shape of the left atrial pressure-volume curve. Study of the effects of various pharmacologic agents on the quantity of regurgitation suggested that drugs causing bradycardia or hypertension without inotropic action would be more effective than agents previously used for the detection of mitral regurgitation in patients.

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PULMONARY ARTERY REPLACEMENT

I. Successful Use of Teflon and Systemic Venous Grafts

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THE suitability of the various available biologic and synthetic vascular graft materials for replacement and bypass grafting of the pulmonary artery has received scant attention in the surgical literature. The only published experience with pulmonary artery replacement was recorded in 1958 by Robinson and his associates.[2] They demonstrated the feasibility of main pulmonary artery replacement by two techniques; one employing cardiopulmonary bypass and elective cardiac arrest. They were somewhat disappointed, however, in the suitability of their graft material. They employed aortic homografts, largely in the fresh state, and their preliminary observations suggested strongly that this type of graft would prove to be unsatisfactory. Their study had been stimulated by a clinical experience with pulmonary artery obstruction due to chronic thrombosis.

Pulmonary artery replacement or bypass may be indicated in clinical situations involving trauma to the pulmonary artery, localized tumor adherence to artery, and segmental arterial obstruction. It also may be found to be useful in the management of certain congenital cardiopulmonary disorders.

The present study was carried out to evaluate the suitability of fresh autogenous systemic vein and of crimped vascular prostheses of Teflon for pulmonary artery replacement.

MATERIAL AND METHODS

Healthy mongrel dogs were used. The weight of the dogs generally was in the 8 to 12 kilogram range. Intravenous Pentothal was utilized for anesthesia. Oxygen was administered through an endotracheal tube by means of a mechanical respirator.

The fresh autogenous systemic vein employed in all replacements was the azygos vein. In the first operation, a portion of the right pulmonary artery was resected and replaced with azygos vein. Because of technical difficulties encountered in working with the proximal right pulmonary artery, we decided to use the left pulmonary artery for all subsequent replacements. In subsequent

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operations, the segment of azygos vein was obtained through a small right third intercostal space incision. The right thoracotomy was closed and the animal was turned and prepared for a left thoracotomy.

Pulmonary artery replacements were carried out through a left thoracotomy in the fourth intercostal space. The pericardium was opened in the area of the origin of the left pulmonary artery. The left pulmonary artery, the main pulmonary artery, and the proximal portion of the right pulmonary artery were dissected free of pericardium and surrounding connective tissue. A Potts coarctation clamp was placed across the main pulmonary artery in a position which isolated the origin of the left pulmonary artery and permitted the maintenance of flow into the right pulmonary artery. A second Potts coarctation clamp was placed across the left pulmonary artery approximately 5 cm. distal to the first clamp and a proximal segment of left pulmonary artery was resected from its origin to, or just beyond, the origin of its first branch.

The resected segment of left pulmonary artery was replaced with a crimped Teflon vascular prosthesis or a segment of fresh autogenous azygos vein. The Teflon graft was a fairly rigid one and all but one of the grafts measured $\frac{3}{8}$ inch in diameter. One graft of $\frac{5}{16}$ inch in diameter was used in one animal because of an abnormally small left pulmonary artery. The right pulmonary artery in this animal appeared to be disproportionately large. The Teflon grafts were essentially the same size as the replaced segment of left pulmonary artery. Occasionally they were slightly larger. All of the Teflon grafts were preclotted. The grafts of fresh azygos vein averaged approximately 2 cm. in length and had essentially the same diameter as the replaced segment of left pulmonary artery.

Continuous, over-and-over sutures of 6-0 arterial silk were used for both anastomoses in all animals. On occasion, additional interrupted sutures were required, usually at the proximal anastomosis. The proximal anastomosis to the main pulmonary artery at the origin of the left pulmonary artery was the more difficult anastomosis, because of an unusual degree of main pulmonary artery friability in this area. No effort was made to close the relatively small opening in the pericardium about the graft. The left thoracotomy was closed in layers and a catheter which was left in place during the closure was aspirated and withdrawn.

RESULTS

Crimped Teflon Grafts.—Left pulmonary artery replacement with crimped Teflon grafts was carried out as described in 17 animals. The fate of the graft was investigated at postmortem examination from 7 to 210 days following operation. Three animals died and 14 were sacrificed. Autopsy was performed from 7 to 24 days after operation in 8 dogs, from 30 to 96 days in 6 dogs, and from 132 to 210 days in 3 dogs.

At autopsy, it was found that 16 of the grafts had remained patent and one was occluded. The animal with the occluded graft was sacrificed 96 days following operation. Occlusion had occurred at both suture lines. In another animal, a slight degree of narrowing of the lumen was found to have occurred when the animal died of pneumonia 19 days after operation. A respiratory tract infection had existed at the time of graft placement. All other grafts

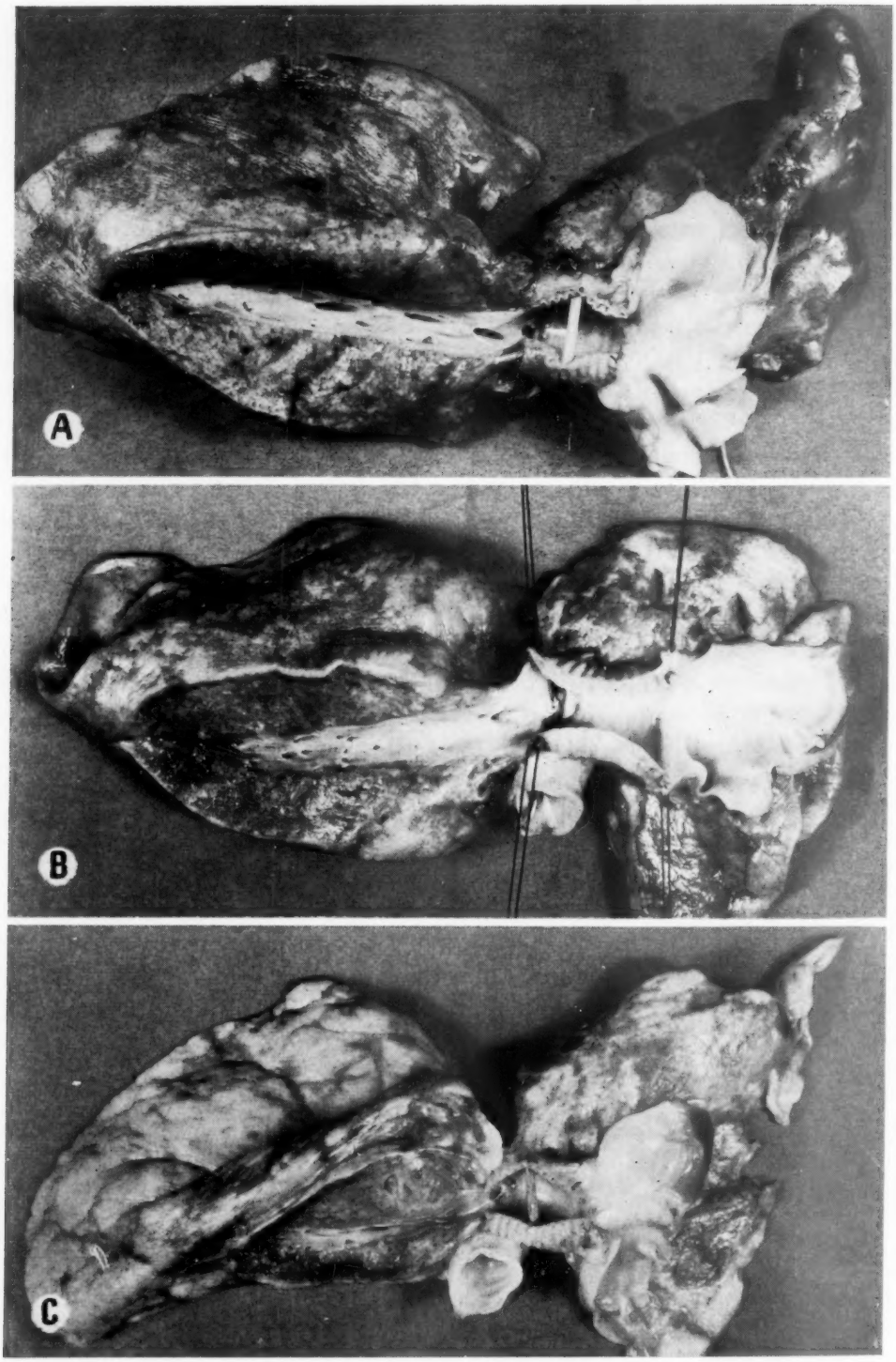

Fig. 1.—Photograph showing postmortem appearance of crimped Teflon vascular grafts used to replace a resected proximal segment of the left pulmonary artery in 3 dogs, *(A)* 35 days after operation, *(B)* 83 days after operation, and *(C)* 132 days after operation.

had widely patent lumens and appeared to have been well tolerated (Fig. 1). The lumen of the grafts was well endothelized and the new lining of the grafts appeared to be relatively thin. The thickness of this lining did not appear to increase with the passage of time either on gross or microscopic examination. On microscopic examination, the surface of the new lining had a straight and smooth, rather than a convoluted appearance. The "valleys" of the crimped graft were filled in with connective tissue and only a relatively thin layer of intima-covered connective tissue was found between the "peaks" of the crimped graft and the lumen (Fig. 2). The Teflon graft was incorporated nicely into the surrounding tissue and there was no evidence of a foreign body reaction.

Fresh Autogenous Systemic Venous Grafts.—Fresh autogenous azygos vein was used for pulmonary artery replacement in 19 animals. The fate of the vein graft was studied at autopsy from 5 to 278 days following operation. Three of the dogs died and 16 were sacrificed. Four dogs were autopsied from 5 to 14 days after operation, 4 dogs from 41 to 82 days, 7 dogs from 117 to 152 days, and 4 dogs from 224 to 278 days.

Seventeen of the 19 grafts were found to be patent on postmortem investigation. In one animal, occlusion of the graft was encountered at sacrifice 65 days following operation. This graft was regarded at the time of operation as a poor one due to main pulmonary artery friability and suture line narrowing. A second graft was found to be occluded at the proximal anastomosis at sacrifice 224 days after operation. Technical difficulties at the time of graft placement also were thought to be related to the failure of the graft in this animal.

All patent grafts appeared to have functioned satisfactorily and all were free of evidence of thrombosis, fibrosis, narrowing, dilatation, and aneurysm formation (Figs. 3 and 4). The grafts remained approximately the same size as the replaced segment of pulmonary artery. The intima of all patent grafts was grossly normal in appearance and the suture lines were well endothelized. Microscopic study of sections taken from a number of patent grafts at varying intervals following operation showed that all of these grafts had continued as living structures and had retained an essentially normal histologic appearance (Fig. 5).

DISCUSSION

The results of this experience with the use of crimped vascular tubes of Teflon for pulmonary artery replacement were quite encouraging. All but one of 17 grafts remained patent during the periods of observation and appeared to function well. All of the grafts were as large as the replaced segment of pulmonary artery, or were slightly larger. In addition, the grafts seemed to be relatively rigid and noncollapsible.

The advantages of the use of synthetic tubes for vascular replacement or bypass are well known. However, most of the investigation of the suitability of the various plastic vascular prostheses has been carried out in high pressure, systemic arterial vascular replacement. Relatively little information is available as yet concerning the usefulness of these materials for vascular replacement in low pressure systems, such as the systemic venous and pulmonary arterial

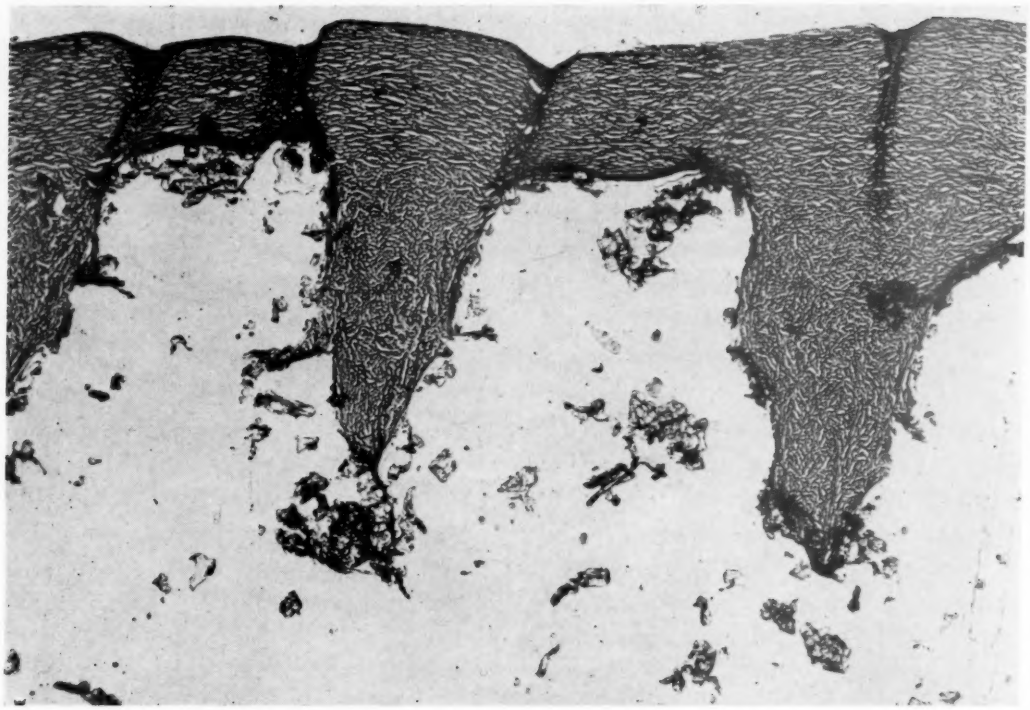

Fig. 2.—Photomicrograph showing the appearance of the new connective tissue and endothelial covering of the crimped Teflon vascular graft pictured in Fig. 1, *C*, 132 days following operation. The Teflon graft has fragmented and fallen away from its lining during fixation and sectioning.

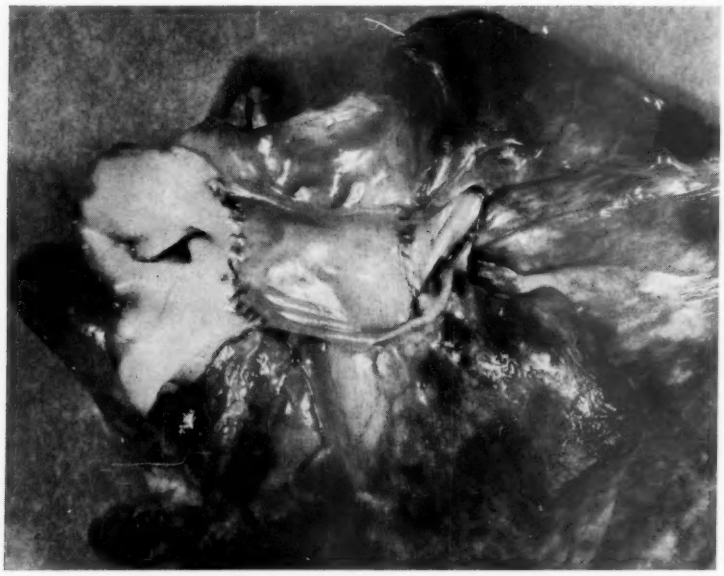

Fig. 3.—Photograph showing the postmortem appearance, 14 days after operation, of a graft of fresh autogenous systemic vein (azygos) employed for replacement of a resected segment of proximal left pulmonary artery. The proximal anastomosis was carried out to the main pulmonary artery in the area of the origin of the left pulmonary artery. The origin of the right pulmonary artery from the main pulmonary artery can be seen.

Fig. 4.—Photograph taken at the time of postmortem examination showing the appearance of the autogenous systemic vein graft in the proximal left pulmonary artery of Dog 995, 117 days after operation, of Dog 993, 124 days after operation, and of Dog 956, 152 days after operation.

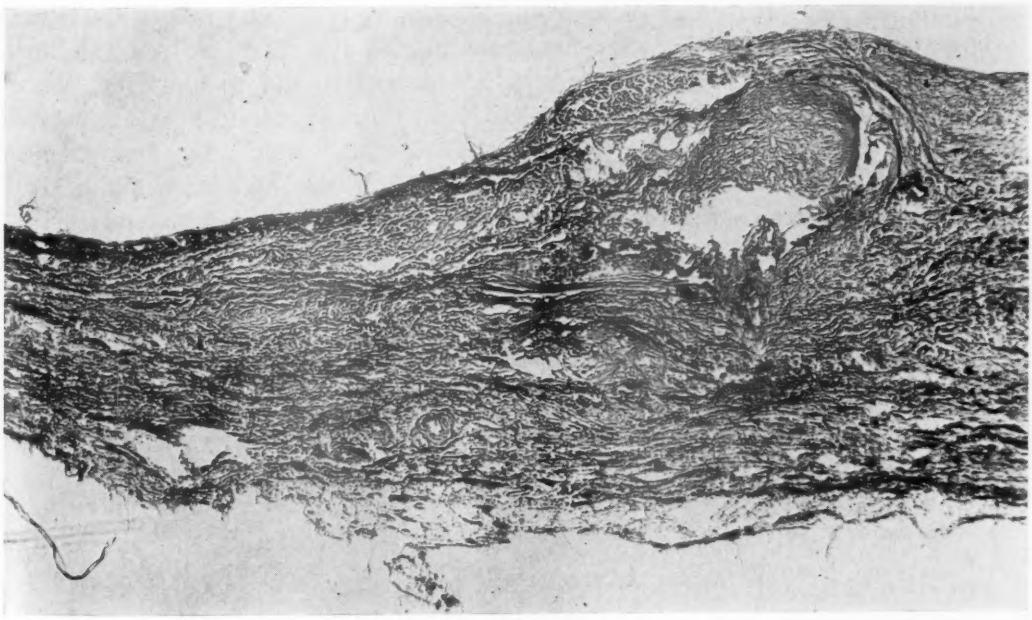

Fig. 5.—Photomicrograph showing the appearance, 3 months after operation, of the line of anastomosis between the thinner autogenous systemic vein graft *(left)* and the thicker pulmonary artery *(right)*.

systems. The results of this study would appear to suggest the suitability of relatively rigid and noncollapsible crimped tubes of Teflon for pulmonary artery replacement when indicated.

The pulmonary arterial system is a comparatively low pressure system with relatively thin walls. It also serves as a conduit for unoxygenated blood. In these respects, it more nearly resembles the systemic venous than the systemic arterial system. The use of autogenous systemic vein for pulmonary artery replacement was suggested by the senior author in 1958.[1]

Seventeen of 19 grafts of fresh autogenous systemic vein, azygos vein, in the pulmonary artery remained patent during the periods of observation and appeared to function satisfactorily. It was suspected that the two failures were due to technical errors at the time of graft placement. The patent grafts retained a normal healthy appearance on both gross and microscopic examination. All patent grafts were free of evidence of thrombus formation, narrowing, or dilatation. These findings would appear to suggest the suitability of fresh autogenous systemic vein for pulmonary artery replacement or bypass.

The reported experience of Robinson and his associates indicating the unsuitability of aortic and arterial homografts for pulmonary artery replacement parallels the experience of a number of investigators with the inadequacy of arterial and aortic homografts for systemic venous replacement.

SUMMARY

The literature relating to experimental pulmonary artery replacement is reviewed briefly. The use of a crimped Teflon vascular prosthesis or a graft of fresh autogenous systemic vein, azygos vein, for proximal left pulmonary artery replacement in 36 dogs is reported. Sixteen of 17 Teflon grafts were found to be patent at the time of postmortem examination from 7 to 210 days following operation, and 17 of 19 azygos vein grafts were found to be patent when studied from 5 to 278 days after operation. Both types of graft appeared to function satisfactorily. The findings of this study would appear to suggest the suitability of both crimped Teflon vascular prostheses and fresh autogenous systemic venous grafts for pulmonary artery replacement or bypass when indicated.

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Pediatric Surgery

CONDUCTED BY MARK M. RAVITCH, M.D.

LYMPHANGIOMA IN INFANCY AND CHILDHOOD

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THE 2 most important lesions which arise from lymphatic channels in children are cystic hygroma and cavernous lymphangioma. Frequently these entities are considered jointly and often little effort is made to differentiate between them. Nevertheless the conditions are basically different in their gross and microscopic characteristics and in their response to therapy. While there is little doubt that combinations of the lesions occur, in the majority of instances the diagnosis of one or the other can be made with accuracy. The typical hygroma arises in the neck and is composed of large, thin-walled cysts which usually intercommunicate and which are lined by a single layer of endothelium. Excision is followed by a high incidence of cure and recurrence is uncommon. Ward and associates[8] reviewed a group of 20 patients with cystic hygromas observed in The Johns Hopkins Hospital during the period 1930-1946 and were unable to find a single incidence of recurrence following surgical removal. It has been our impression that the course of the patient with the cavernous type of lymphangioma is notably different and presents a greater problem in management.

PATHOLOGY

Several different types of lesions may arise from lymphatic channels. The lesions vary from cystic forms, which are quite benign and are consistently associated with an excellent prognosis, to the more solid tumors which are frequently characterized by recurrence following primary excision. The types may be classified as follows: (1) simple lymphangiomas, (2) cystic hygroma, (3) cavernous lymphangioma, (4) lymphangiohemangioma, and (5) lymphangiosarcoma.

Simple lymphangioma is an uncommon and generally insignificant lesion. It is usually small and superficial with an appearance similar to that of an ordinary wart. Histologically such lesions are composed of simple dilations of the subepithelial lymphatic channels.

Cystic hygromas arise from the same primordia as do normal lymph vessels. These lesions are found chiefly in the neck but may also occur in the

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axilla and retroperitoneal tissues. Grossly the cysts are thin walled and multiloculated. They contain lymph which has not been permitted to drain normally into the lymphatic system. Microscopically such cysts are lined with flattened endothelial cells supported by a stroma of fibrous tissue (Fig. 1, *A*). Goetsch[2] considers the cystic hygroma to be a benign, true neoplastic tumor of lymphatic origin. Excision of the cystic hygroma is usually followed by cure.

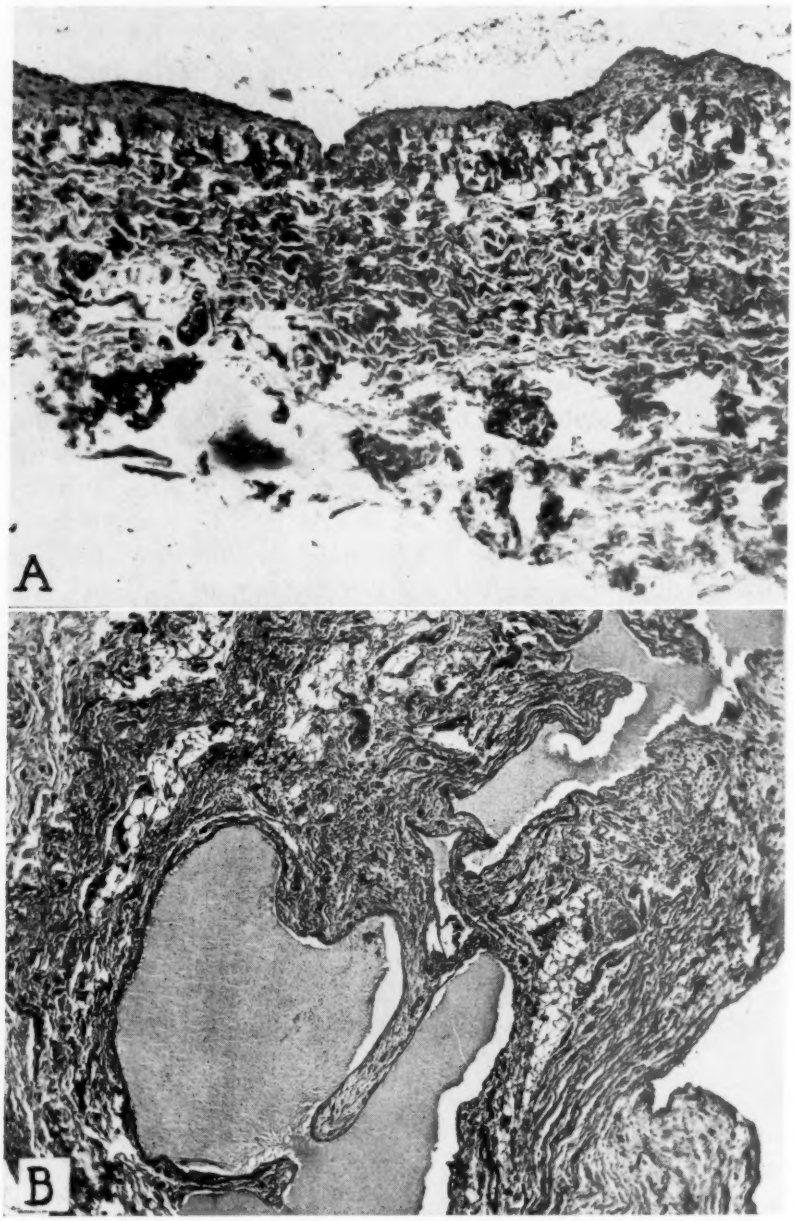

Fig. 1.—*A*, Photomicrograph of wall of typical cystic hygroma. A single layer of endothelial cells overlies a fibrous stroma. Grossly the lesion consisted of a large, single cyst. (Reduced from ×75.) *B*, Photomicrograph of typical cavernous lymphangioma. Multiple microscopic cysts are present and are lined with endothelium. The fibrous tissue stroma is abundant. (Section taken from patient shown in Fig. 2.) (Reduced from ×50.)

Cavernous lymphangiomas comprise the largest group of solid neoplasms of lymphatic origin. They occur in the skin and subcutaneous tissue and are also found in other areas such as the salivary glands and tongue.

Their size varies greatly from small, circumscribed lesions to those which may involve an entire extremity and adjacent areas. They are diffuse, spongy, compressible masses, the margins of which are often difficult to delineate. The microscopic appearance varies considerably but consists chiefly of multiple, dilated lymph channels lined with single or multiple layers of endothelial cells (Fig. 1, *B*). The fibrous stroma may be either abundant or scanty. These tumors are noted for their invasive tendencies and they frequently penetrate underlying muscle and other contiguous structures.

Lymphangiohemangiomas consist of a combination of blood- and lymph-containing channels. These lesions are quite similar to cavernous lymphangiomas except that some of the spaces are filled with erythrocytes and are presumably in direct communication with the vascular system.

Watson and McCarthy[9] have emphasized the necessity for differentiation between cystic hygroma and cavernous lymphangioma. Both these lesions tend to occur in infants and in certain anatomic sites. The diagnosis depends on the appearance of the lesion at operation as well as its microscopic characteristics. The cystic hygroma is composed of large, multiloculated cysts which are more or less clearly delineated. Histologically the endothelium in a cystic hygroma tends to be more flattened, with less fibrous stroma, than that in a cavernous lymphangioma (Fig. 1, *A* and *B*).

In some instances it is impossible to state categorically whether the vascular elements in the tumor are lymphangiomatous channels into which bleeding has occurred or whether a hemangioma is present as well. If lymphangiomatous tissue was the strongly predominant type, the lesion was included among the cavernous lymphangiomas in the present study.

The distinction between lymphangioma and lymphangiosarcoma may be difficult to make. Lymphangiosarcoma is rare and this diagnosis is generally reserved for lesions showing either gross or histologic evidence of malignancy. It represents a type of tumor which is highly invasive and which scarcely needs to be considered in children. Stewart and Treves[6] as well as Stout[7] have reported several cases of this type occurring in the upper extremity following radical mastectomy.

CLINICAL MATERIAL

During the period 1930-1958 27 patients with cavernous lymphangioma in infancy and childhood were observed at The Johns Hopkins Hospital. Of the group 18 (67 per cent) were noted to have had the lesion at birth. Of further significance is the fact that in all patients except 1 (96 per cent) lymphangioma had been present by the age of 1 year. Sex, race, and family history were not found to be factors of significance (Table I). The most frequent site of the lesion was the head and neck (52 per cent), followed by the lower extremity

(30 per cent), arms and axilla (11 per cent), and trunk (7 per cent). The individual patients are presented in Table I and the localization of the anatomic sites is shown in Table II.

All patients reported in the present study were classified as having cavernous lymphangioma and no patients with cystic hygroma were included. The treatment consisted of surgical excision. Eight patients received radiation therapy in addition. The high incidence of local recurrence associated with this lesion is illustrated by the fact that a total of 88 surgical procedures were performed in the group of 27 patients. Two patients died. One was a 2-year-old child who died as a result of extensive cellulitis which occurred 8 months following operation in an area of incompletely removed lymphangioma. The other was a 7-week-old infant with a massive bilateral lymphangioma of the neck. Death in this instance was caused by respiratory obstruction in the postoperative period. Of the 25 remaining patients, 13 are free of disease and represent apparent cures. Six others may have recurrences on clinical examination but these are minor and show no evidence of extension. The remaining patients either have advanced involvement far beyond the scope of operative removal, have declined further operation, or are lost to follow-up (Table I).

The records of 4 children with cavernous lymphangioma in the present series are presented in detail and are chosen as illustrations of representative problems encountered in the management of these lesions.

CASE REPORTS

CASE 1.—A 2-month-old female infant was admitted with the history of a small mass near the left ankle which had been present since birth. On examination a soft, spongy lesion 2 cm. in diameter was present in the subcutaneous tissue of the left ankle near the medial malleolus. The mass was nontender and there was no involvement of the overlying skin. It was excised and the pathologic diagnosis was cavernous lymphangioma. On examination 1 month later another mass was noted beneath the scar. The child was again admitted and a large area of skin and underlying tissue was excised. A split-thickness skin graft was applied. Histologic section of the specimen showed recurrent (or inadequately excised) cavernous lymphangioma. The child has been followed since for 3 years with no evidence of recurrence.

Although the original lesion was small and its treatment was regarded as simple, this patient illustrates the problem which follows inadequate initial removal. Wide excision with application of a skin graft was followed by cure. It is probable that this should have been employed at the first operation as a basic principle of surgical treatment.

CASE 2.—A 4-year-old girl was admitted with a history of a small mass present at birth in the subcutaneous tissue of the left lower abdominal quadrant. The mass became less prominent as she developed, but 1 week prior to admission another was noted in the soft tissue of the left anterior thigh. This lesion was 6 cm. in diameter, soft, and well circumscribed. It was excised and the microscopic diagnosis was cavernous lymphangioma. Following the operation repeated aspiration of the wound was necessary because of recurrent serous effusion. The appearance of the area surrounding the incision suggested recurrence of the lesion (Fig. 2). A diagnosis of incomplete removal (or recurrence) was made and the thigh was re-explored. The subcutaneous tissue of the left thigh and lower left quadrant of the abdomen was found to be extensively involved with multiple, small, fluid-filled cystic spaces. The process extended into the sartorius muscle which was also involved and which was removed with the specimen. The defect was covered with a split-thickness skin graft. At the time of the second operation it was felt that all the involved tissue was excised.

The child has been asymptomatic and free of recurrence for 7 years. This patient represents another example of inadequate initial excision of surrounding tissue. The more extensive second operation has been followed by an apparent cure.

Fig. 2.—(Case 2.) Photograph illustrating recurrence of cavernous lymphangioma beneath the scar of a previous incision. A wide excision with application of a split-thickness skin graft was performed. The patient has been well and free of recurrence for the past 7 years.

CASE 3.—A 1-year-old male was admitted with the history of an enlarging mass in the right axilla first noted 4 months previously. On examination a soft mass 8 by 10 cm. in diameter was found in the right axilla with extension to the chest wall. An operation revealed the entire axilla to be filled with a massive cystic tumor which was adherent to the brachial plexus and axillary vessels. The involved tissue and overlying skin were excised and a split-thickness skin graft was applied. Five months later a recurrence was noted in and beneath the graft (Fig. 3, *A*). This subsequently became infected, producing extensive cellulitis and systemic symptoms requiring antibiotic therapy. Following subsidence of the acute infection it was apparent that the extent of recurrence required a shoulder girdle amputation and this was performed (Fig. 3, *B*). There was no evidence of further difficulty until 4 years later when a recurrence in the subcutaneous tissue of the right side of the neck posterior to the sternomastoid muscle was first noted (Fig. 3, *C*). A modified radical neck dissection was performed with excision of the involved tissue. The child has been followed for over 3 years, is free of recurrence, and has developed normally (Fig. 3, *D*).

This case illustrates the necessity of repeated examination following operation and the need for further excision therapy in the event of subsequent extension. It also emphasizes the fact that recurrences may occur after prolonged periods of apparent cure.

CASE 4.—A female child was first examined in 1951 at the age of 6 weeks with the history of a mass in the right lower quadrant present since birth. On examination a large mass was found extending from the right flank into the right lower quadrant. Three successive operations were performed with partial excision, but extension into the retroperitoneal tissues prevented complete removal. Two years later the child returned with a massive involvement of the right lower quadrant and anterolateral thigh with tumor. Much of the neoplasm was removed by operation, but infiltration of the retroperitoneal structures prevented complete excision. In 1955 the patient was found to have a recurrence of the lesion in the right lower quadrant and also in the right gluteal region. In 1958 she was readmitted with the history of recent ulceration of the gluteal recurrence, evidence of marked cellulitis, and a chronic, malodorous discharge requiring frequent dressings. Examination showed ulcerated and fungating areas of tumor over the right gluteal region and a firm mass filling most of the right lower quadrant (Fig. 4, *A*). The ulcerated area was excised and the soft tissues were approximated with sutures of stainless steel wire. The course following operation was gratifying to both the child and her family (Fig. 4, *B*). There was no further

TABLE I. CAVERNOUS LYMPHANGIOMA

	RACE AND SEX	AGE AT APPEARANCE	AGE EXAMINED	SITE	NUMBER OF OPERATIONS*	OTHER TREATMENT	EXISTING RECURRENCE	REMARKS
1	NF	Birth	6 wk.	Right flank and buttock	6		Yes	Extension to retroperitoneal tissues; multiple excision for cellulitis in ulcerated recurrence
2	WF	Birth	19 mo.	Right neck and nasopharynx	2	X-ray	No	Apparent cure despite incomplete removal
3	NF	3 wk.	16 mo.	Left posterior auricular area	3		No	
4	WF	7 days	3 mo.	Left ankle	2		No	
5	WM	Birth	4 mo.	Above left ear	1		Yes quiescent	
6	WF	Birth	5 mo.	Right arm, axilla and chest; left toes	4		Yes	Lost in follow-up
7	WM	Birth	12 days	Entire left leg and buttock	1		No	Hindquarter amputation
8	NM	7 mo.	17 mo.	Right arm and axilla	3		No	
9	NF	3 mo.	2½ yr.	Left lower abdomen and femoral area	2		Yes	Lost in follow-up
10	WM	Birth	11 yr.	Left thigh	4		Yes	Elephantiasis, left leg
11	WF	Birth	4 yr.	Tongue	1	X-ray	Yes quiescent	
12	NM	1 yr.	5 yr.	Tongue	1	X-ray	Yes quiescent	
13	WF	6 yr.	6 yr.	Floor of mouth	5		No	Submental approach on fifth operation
14	WM	2 wk.	1½ yr.	Tongue	2		No	
15	NF	Birth	6 yr.	Tongue and submental area	3	X-ray	Yes quiescent	Submental approach at third operation
16	WM	Birth	4 mo.	Right neck	1	X-ray	No	Facial nerve paralysis, transitory
17	WM	Birth	2 yr.	Bilateral buttock	1	X-ray	(Death)	Death due to infection 8 mo. postoperatively
18	WM	Birth	6 wk.	Right leg, flank and abdomen	15		Yes	

TABLE I—CONT'D

	RACE AND SEX	AGE AT APPEARANCE	AGE EXAMINED	SITE	NUMBER OF OPERATIONS*	OTHER TREATMENT	EXISTING RECURRENCE	REMARKS
19	WF	3 mo.	16 mo.	Floor of mouth	3		No	Submental approach at third operation
20	NM	Birth	11 mo.	Left upper lip	4		Yes quiescent	
21	WF	Birth	21 mo.	Left thigh	7		Yes	Intra-abdominal extension. No follow-up
22	WM	Birth	8 mo.	Left parotid	3	X-ray	No	Facial nerve paralysis
23	WF	Birth	3 wk.	Right axilla, chest and arm	8	X-ray	No	Forequarter amputation
24	NM	Birth	4 mo.	Right neck	2		No	
25	WF	8 mo.	1 yr.	Left thigh	1		Yes	Lost in follow-up
26	NM	Birth	7 wk.	Bilateral neck	1		(Death)	Death due to postoperative respiratory obstruction
27	WF	Birth	3 yr.	Left thigh	2		No	

*Planned staged procedures counted as single operation.

TABLE II. ANATOMIC DISTRIBUTION OF CAVERNOUS LYMPHANGIOMA

Head and neck	Tongue		4	
	Neck		4	
	Floor of mouth		2	
	Lip		1	
	Parotid		1	
	Preauricular		1	
	Postauricular		1	
		Total	14	(52%)
Lower extremity	Thigh		4	
	Thigh and abdomen		2	
	Thigh and buttock		1	
	Leg		1	
		Total	8	(30%)
Upper extremity	Arm, axilla, and chest		2	
	Arm and axilla		1	
		Total	3	(11%)
Trunk	Trunk, including buttocks		2	(7%)
Total			27	

cellulitis or odorous discharge and no dressings were required. A year later a recurrent lesion was excised for the same reason as before and with a similar result. Currently the child continues to have residual neoplasm but no troublesome symptoms or ulceration.

This patient represents an example of the significant palliation which may follow the local excision of ulcerated areas of lymphangioma. It is interesting that such a wound will heal satisfactorily with residual tumor in the margins. The relief offered such patients is often impressive and usually greater than might be expected.

DISCUSSION

Congenital lesions of the lymphatic system are best approached by a consideration of the basic work of Sabin[5] concerning the embryology and development of the lymphatics. These classic studies demonstrated that the lymphatic

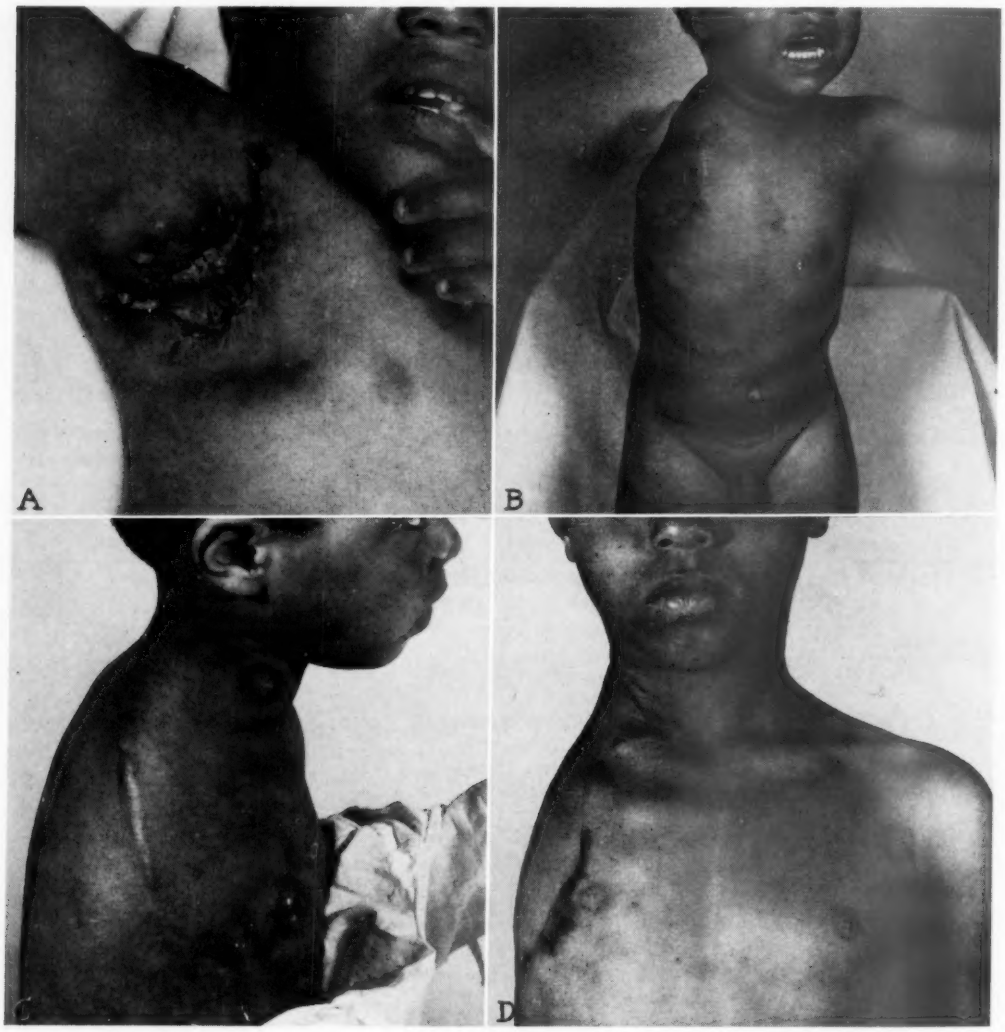

Fig. 3.—(Case 3.) *A*, Photograph of axillary cavernous lymphangioma. A mass in this region had been excised previously and had recurred. A shoulder girdle amputation was necessary to remove the involved area completely. *B*, Photograph of patient at the age of 2 years following shoulder girdle amputation. *C*, Photograph 4 years later showing a recurrence of the lesion in the right side of the neck posterior to the sternomastoid muscle. *D*, Photograph following modified right radical neck dissection. The child has remained well and free of recurrence for the past 3 years.

system begins as a series of endothelial buds which arise directly from the veins and form small plexuses which develop into lymph sacs. Sabin showed further that all lymphatics begin as capillaries and that their method of growth is by the sprouting of the protoplasm and by nuclear division of the endothelium of the capillary wall. Through this origin there is a continuous growth and invasion of the body by lymphatic channels from the primary sprouts which emerge from

the veins and ultimately form the peripheral lymphatic capillaries. The large, multiloculated cystic hygroma is often regarded as the enlargement of lymphatic spaces secondary to failure of the lymphatics to empty normally into the venous system. Goetsch[2] considers this lesion to be a true benign neoplasm and presents histologic evidence supporting this view. The more solid type of cavernous lymphangioma is properly regarded as an area of embryonic lymphatic tissue which retains its powers of peripheral growth by endothelial proliferation of multiple, tiny, lymphatic cysts. These proceed to multiply in an uncontrolled and disorderly fashion with a tendency to penetrate and destroy surrounding tissue. Combinations of the 2 lesions occur, although in the majority of cases a differentiation between the types comprised of large, thin-walled cysts (cystic hygromas) and the more solid, small to microscopic cysts (cavernous lymphan-

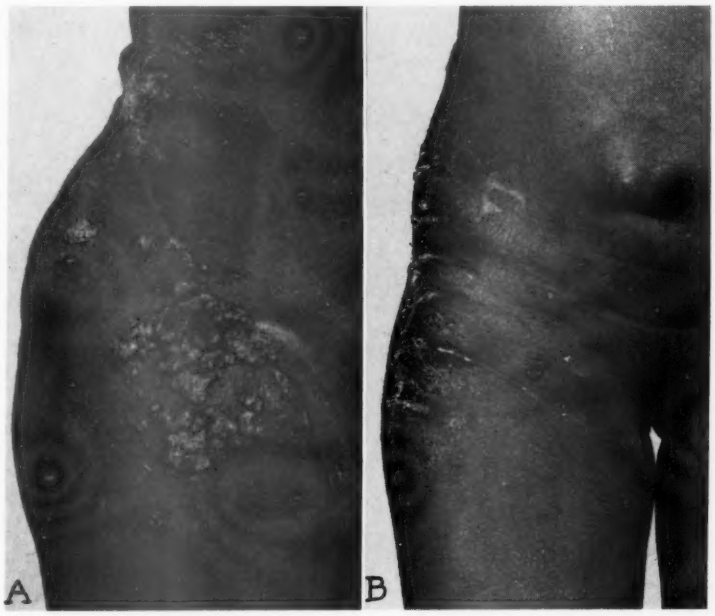

Fig. 4.—(Case 4.) *A*, Photograph of child with advanced cavernous lymphangioma involving the right lower quadrant, thigh, buttock, and retroperitoneal tissues. Ulceration of the skin by the tumor produced foul drainage associated with an extensive cellulitis and marked systemic symptoms. *B*, An excision of the ulcerated area and approximation of the tissues with removable sutures of stainless steel produced a gratifying palliative result.

giomas) can be made. Briggs and his associates[1] have previously discussed the division of these lesions, and the importance of an accurate histologic diagnosis is reflected in the operative management and in the prognosis.

In the present study, 96 per cent of the lesions were noted in the first year of life, a fact which lends strong support to the argument for congenital origin of such lesions. The clinical behavior of the cavernous lymphangioma is more complex and is associated with greater problems than is that of its more benign counterpart, the cystic hygroma. The definite tendency of the former lesion to recur following local excision constitutes the most difficult problem in its management. The study of this group of patients has demonstrated the necessity for an appreciation of the fact that cavernous lymphangioma in childhood

is a serious problem and one which demands early and extensive excisional therapy if the best results are to be obtained. Wide excision of the involved area with a margin of normal tissue and often with removal of the overlying skin is the preferred approach. In discussing the mixed angiomas of childhood, Ravitch[5] has emphasized the fact that "early radical excision offers the best chance of cure with ultimate preservation of maximum function and minimum

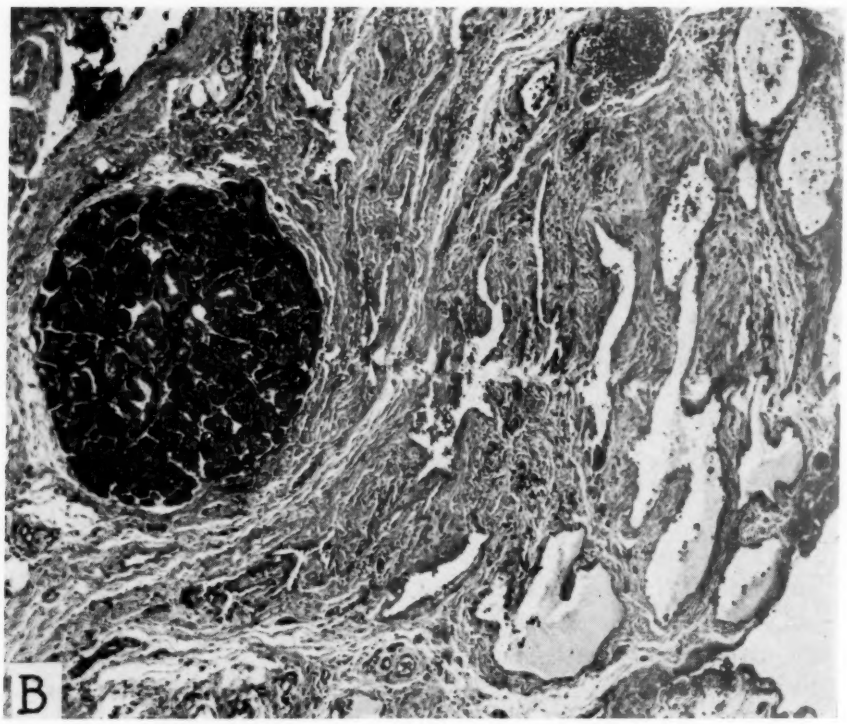

Fig. 5.—*A*, Photograph of child with cavernous lymphangioma arising behind the left ear and extending anteriorly. An initial excision was inadequate but further excision has produced an apparent cure. *B*, Photomicrograph showing extension of the cavernous lymphangioma into the parotid gland. (Reduced from ×75.)

cosmetic deformity." Careful and repeated examination in the postoperative period, particularly in the first year, is mandatory and should any significant recurrence appear, further excision is indicated. The role of x-ray therapy has been a controversial subject in the literature, and although it was employed in the management of 8 of the patients in this study, its effect could not be shown to have significantly influenced the results.

The results of treatment vary according to the size of the lesion and the site. Lesions occurring in the upper leg and lower trunk are the most difficult to remove successfully because they are often the largest ones encountered and also because they tend to extend proximally into the retroperitoneal tissues. Large neoplasms of the upper arm and axilla and of the neck are similarly

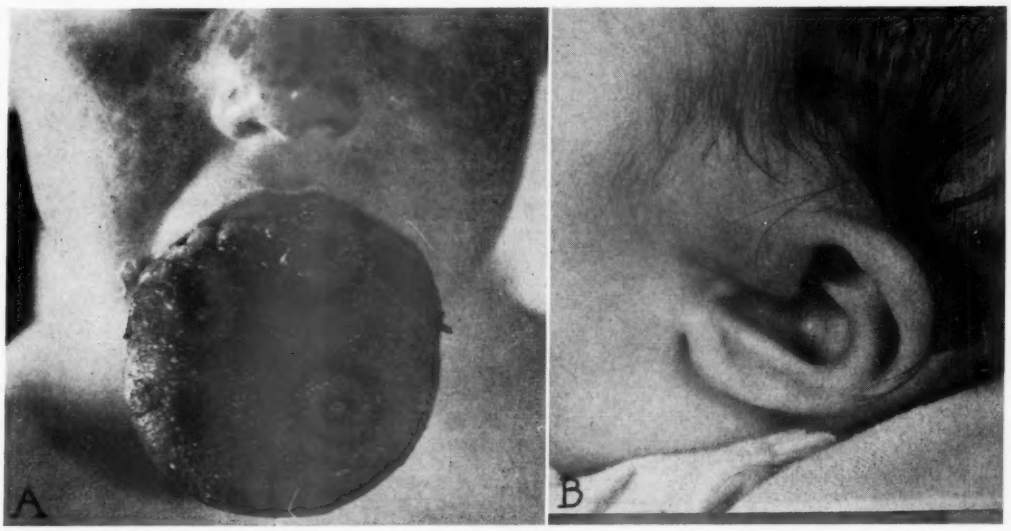

Fig. 6.—Photographs of cavernous lymphangiomas of tongue *(A)* and preauricular region *(B)*.

difficult, although results of treatment are somewhat better. Lesions associated with the parotid gland (Fig. 5) are prone to recur, and extensive dissection may lead to facial nerve damage. The small lesions of the floor of the mouth invariably recurred following simple intraoral dissection, but were satisfactorily controlled by submental excision. There have been at least 2 patients in this study in whom excision has been curative in spite of residual tumor which was necessarily left at the time of operation. Similar observations have been made by Gross and Hurwitt.[3]

A further observation has been severe infection in areas of recurrence, particularly when associated with ulceration. It has been the cause of death in 1 patient and a difficult complication in several others. When infection is present antibiotics usually produce a satisfactory response, although reinfection is common. In such instances it is at times feasible to perform further excision of the involved tissue with primary closure even when total or curative excision is not possible. Such palliation can produce gratifying results.

SUMMARY

A group of 27 infants and young children with lymphangioma of the cavernous type has been reviewed. The pathology, diagnosis, treatment, and prognosis are discussed. Emphasis is placed upon the importance of differentiating cavernous lymphangioma from the more common cystic hygroma inasmuch as the behavior of the 2 conditions is significantly different. The study demonstrates the strong tendency of the cavernous lymphangioma to invade and to recur. Extensive initial excision with careful postoperative observation is the recommended method of management.

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SMALL BOWEL ATRESIA: TREATMENT BY RESECTION AND PRIMARY ASEPTIC ANASTOMOSIS

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SMALL bowel atresia is one of the more common congenital anomalies causing intestinal obstruction in the newborn. A recent study of 163 cases of neonatal intestinal obstruction disclosed that atresia and stenosis were the most common causes, accounting for more than one quarter of the cases.[4] Hirschsprung's disease was the next most frequent cause of obstructive symptoms in newborn infants. The successful management of small bowel atresia remains a challenge to the attending surgeon for associated anomalies are unusual. Provided that intestinal continuity is restored, patients with small bowel atresia become normal children.

Until 1950, only 20 surviving patients were reported in the world literature.[14] In recent years major advances in the management of intravenous fluids, serum electrolytes, anesthesia, and antibiotics have contributed to a lower mortality. Another favorable factor is more widespread understanding of the condition and this has prompted earlier referral of the patients for operation. Several methods of operative management have been suggested, including side-to-side and side-to-end anastomosis and temporary ileostomy. In our experience the single-layered, end-to-end anastomosis has proved to be a most satisfactory technique. This report summarizes the results of 11 cases managed by this method.

DIAGNOSIS

The infant with small bowel atresia develops progressive symptoms of intestinal obstruction within a few hours after birth. Swallowed air rapidly fills the gastrointestinal tract proximal to the obstruction, causing abdominal distention and vomiting of bile-stained material within 24 hours. If the abdominal distention progresses, the diaphragm is elevated and respiratory activity is limited. Distended loops of intestine with fluid levels are seen in supine and upright abdominal roentgenograms (Fig. 1). A barium enema is indicated to rule out Hirschsprung's disease, which is a common cause of intestinal obstruction in infancy.[4] In a recent study of 64 infants with Hirschsprung's disease, 73 per cent presented symptoms and signs of neonatal intestinal obstruction. Plain roentgenograms of the abdomen were available from 42 neonatal infants with Hirschsprung's disease. In 36 cases, no specific diagnosis could be made from the plain films (Fig. 2). Thus it was evident that from history, clinical characteristics, and plain abdominal roentgenograms, these conditions frequently

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Fig. 1.

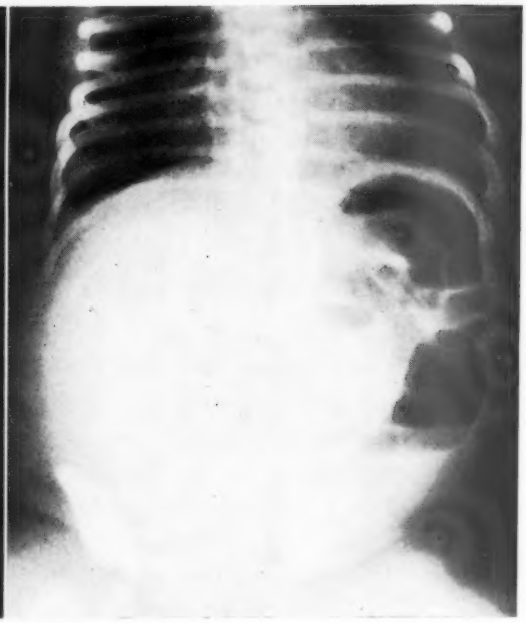

Fig. 2.

Fig. 1.—Photograph of supine abdominal roentgenogram of a newborn infant with small bowel atresia. Distended loops of intestine are filled with swallowed air.

Fig. 2.—Photograph of erect abdominal roentgenogram of a newborn infant with Hirschsprung's disease. Distended loops of intestine have fluid levels.

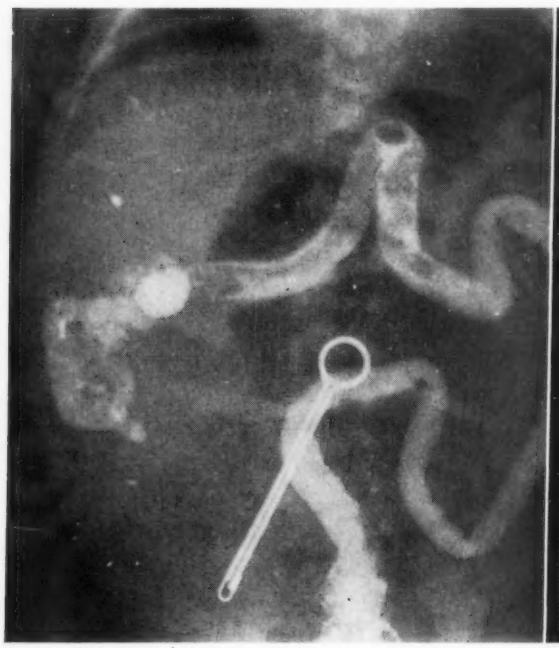

Fig. 3.

Fig. 4.

Fig. 3.—Photograph of a roentgenogram of the same infant with Hirschsprung's disease taken during a barium enema. The large diameter of cecum and ascending colon is noted.

Fig. 4.—Photograph of a barium enema roentgenogram of the infant with small bowel atresia. The small diameter of the colon is noted.

are indistinguishable unless a barium enema is performed (Fig. 3). A dilated colon rules out atresia or other lesions producing small bowel obstruction. In small bowel atresia the colon is small in caliber but patent and in a normal position (Fig. 4). As multiple atretic areas are not uncommon, it is imperative for the surgeon to demonstrate by inspection the patency of the intestinal tract below the atresia. The small intestine can be readily examined. But the colon, being in part retroperitoneal, cannot be easily visualized completely. A preoperative barium enema outlining an intact but small-caliber colon relieves the surgeon of this difficult task.

Evidence of dehydration may be found if vomiting is severe, even as early as 24 hours after birth. Derangement of the serum electrolyte pattern rarely occurs unless the vomiting continues longer than 48 hours. It is wise to delay operation until dehydration and the electrolyte derangement have been adequately compensated.

OPERATIVE TREATMENT

Under local anesthesia the saphenous vein at the ankle or the basilic vein in the antecubital space is exposed and a polyethylene catheter is inserted to provide an adequate, dependable means of replacing blood loss during the operation. The nasogastric tube inserted shortly after the patient's admission must be inspected frequently to determine its patency and it is left in place during the operation to maintain gastric decompression, thus averting regurgitation and providing more abdominal space for the surgeon. Delay of operation beyond the few hours required for adequate preparation of the patient may be dangerous for, while the most likely diagnosis is atresia, the lesion may be volvulus or a congenital band producing obstruction, and unnecessary delay may permit perforation and the development of peritonitis. The success of this operation is related to numerous factors, not the least of which are the knowledge, experience, and skill of the surgeon. Successful management requires exact attention to detail, a gentle technique, and small, delicate instruments.

Although the best technical conditions for the operation are obtained under general anesthesia, decision as to the type of anesthesia is determined by the infant's status. A premature neonate tolerates general anesthesia poorly and tends to lose spontaneous respiratory activity even in the lighter planes of anesthesia. An infant who has sustained considerable fluid and electrolyte loss is prone to develop cardiovascular collapse when general anesthetics are administered. Another hazard of general anesthesia is the limited respiratory reserve because of the elevated diaphragm associated with massive distention, or because of atelectasis from the aspiration of vomitus. Any combination of these unusual conditions may make general anesthesia an unacceptable risk. Local anesthesia is accomplished by the infiltration of 0.5 per cent procaine into the skin, subcutaneous tissue, fascial layers, and peritoneum. The infant is restrained in the supine position and oxygen administered by mask to facilitate respiratory exchange under the conditions of abdominal distention and atelectasis. As respiratory distress from the high diaphragm is relieved, the child remains quiet.

The preferred incision is 5 to 6 cm. long in the midabdomen over the right rectus muscle. The muscle fibers are retracted laterally. The entire small intestine is delivered through the incision in the anterior abdominal wall. The intestine proximal to the atresia is widely dilated and filled with meconium and air (Fig. 5). This blind end may be 4 to 7 cm. in diameter with thickening and hypertrophy of the wall. Gradually, dilatation decreases as the intestine is followed proximally until 15 cm. from the blind end, where the diameter of

Fig. 5.

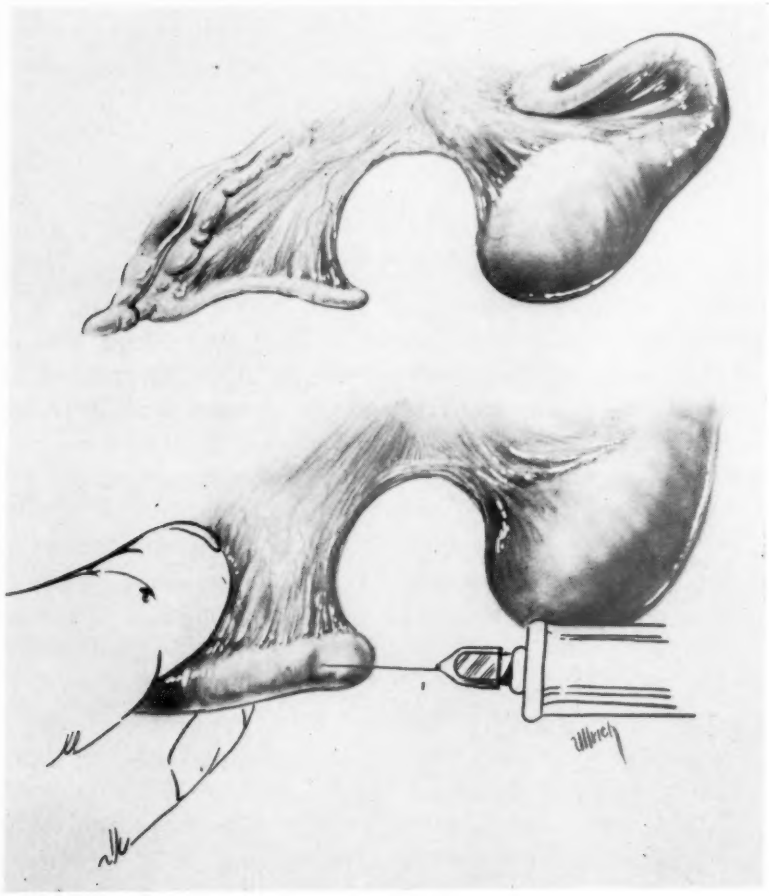

Fig. 6.

Fig. 5.—The blind end of the small bowel proximal to the atresia is widely dilated, being filled with meconium and gas. The blood supply to this segment of bowel may be anomalous. Decompression of the proximal bowel is readily accomplished through the dilated end which is resected.

Fig. 6.—The distal blind end is collapsed. By means of a small syringe and needle, the lumen is distended with saline.

the bowel is about 2 cm. The intestine beyond the atresia is small, atrophic, and empty. The 2 blind ends may be connected by a cordlike structure or may be completely separated. Distention of the empty small bowel is accomplished by injection of 5 to 10 ml. of sterile saline by means of a needle and syringe (Fig. 6). The patency of the intestine down through the ileocecal valve is

demonstrated by milking the injected saline through the intestine. Provided a barium enema has been given, inspection of the colon will be unnecessary. Experimental evidence has suggested that the massively dilated intestine is unlikely to regain its normal caliber and effective peristaltic action.[11] For this reason the dilated, hypertrophic intestine proximal to the obstruction is resected for a distance of 10 to 15 cm. back from the blind end. Technically, the operation is facilitated if all the intestine proximal to the obstruction is aspirated to decompress the bowel of gas and secretions. A device to accomplish this aspiration effectively has been described.[15] The decompression of loops of intestine facilitates closure of the abdominal incision. Postoperatively, intestinal function returns more rapidly if the loops of bowel are not distended.

The site for the resection is chosen where the caliber of the bowel is nearly normal (Fig. 7). Two small hemostatic forceps are placed across the intestine and a scalpel is used to divide the bowel between clamps. Care should be taken in dividing the mesenteric blood vessels to stay near the bowel wall. Without this precaution the blood supply to the remaining intestine may be damaged. Similar hemostatic forceps are placed across the intestine beyond the atresia (Fig. 8). The caliber of the intestine may be enlarged to more nearly that proximal to the atresia by distending the lumen with sterile saline before placing the clamp across the bowel. Also, the clamp may be placed obliquely to obtain a larger lumen cut surface. An end-to-end anastomosis is then performed between the 2 clamped ends of bowel. Halsted sutures (No. 5-0 or No. 6-0 silk) are placed posteriorly in a single layer and not tied (Fig. 9). The anterior layer is also placed before the clamps are removed, with silk passing under the points of the instruments to permit removal of the clamps without opening the lumen of the bowel (Fig. 10). The sutures are placed slightly farther apart on the larger side of the anastomosis to make up for the disparity in diameters. As the sutures are placed, care is taken that they go only through the serosa and muscular coats. Any sutures that enter the mucosa are likely to lead to leakage of intestinal contents into the peritoneal cavity. If the clamps are carefully removed, the lumen remains sealed by the rim of intestine that is crushed in the hemostatic forceps (Fig. 11). The sutures are tied, with care being taken to turn the corners of the intestine in properly (Fig. 12). The lumen of the intestine is opened by massaging the area of the anastomosis between the fingers and breaking the seal of the crushed ends of the bowel (Fig. 13). A patent lumen may be demonstrated by manually pushing fluid and air through the anastomosis. The defect in the mesentery is closed and the intestine is returned to the abdominal cavity. Interrupted sutures of No. 5-0 silk are used to close the peritoneum and anterior rectus fascia in layers. Subcutaneous fascia is closed with interrupted No. 6-0 silk sutures and the skin margins are approximated with a continuous subcuticular suture of No. 5-0 plain catgut. A collodion dressing is applied. The collodion dressing is particularly advantageous in the small infant since the abdomen is easier to examine without a bulky dressing. Also soiled diapers are likely to contaminate a gauze dressing.

Postoperatively, intermittent nasogastric suction is maintained until regular peristaltic activity is evident by auscultation and the passage of stools. Intravenous fluids are administered as indicated to assure adequate urinary output and to replace losses from the nasogastric tube. Provided dehydration has been corrected preoperatively, the fluid intake should be strictly limited to the basic physiologic needs. A safe and accurate method is to administer intravenous fluids on the basis of the body area.[16] The surface area of the body may be

Fig. 7.

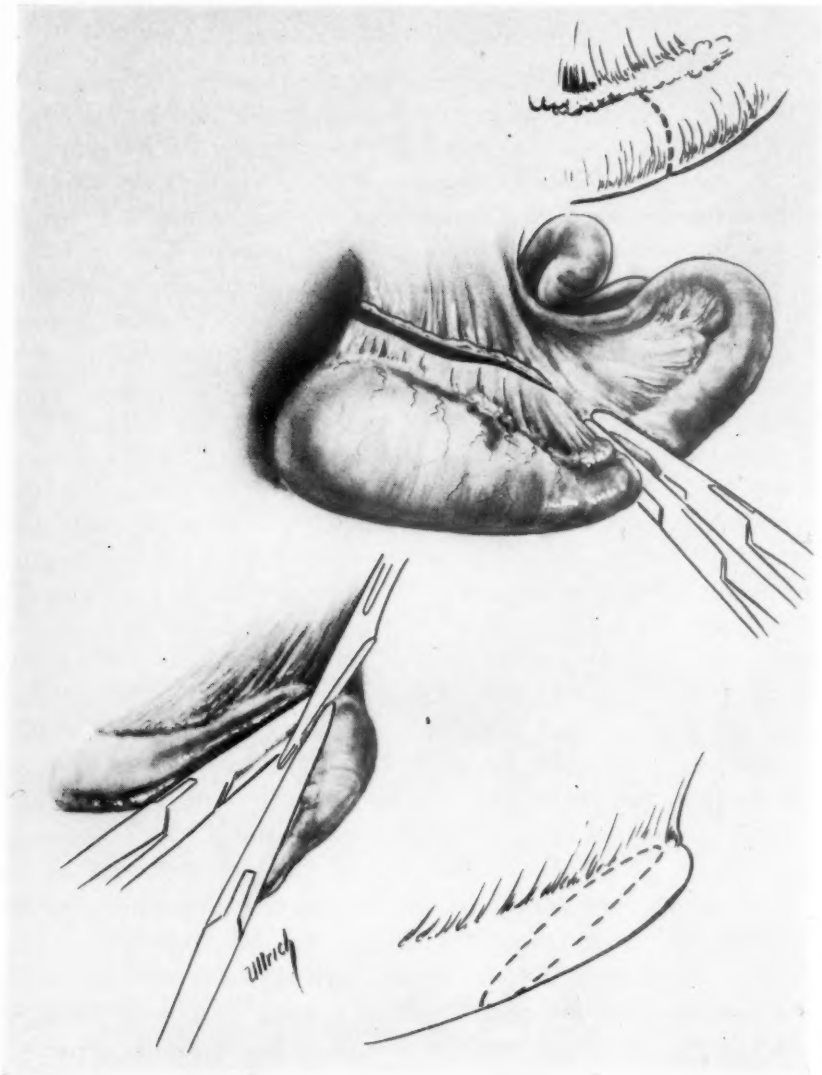

Fig. 8.

Fig. 7.—The bulbous proximal end is excised, necessitating removal of 10 to 20 cm. of ileum. The chronically dilated segment fails to function properly. The site for placing of the clamps is chosen where the diameter of the bowel is nearly normal.

Fig. 8.—After the distal segment is distended with saline, clamps are placed obliquely across the bowel to increase the diameter available for anastomosis. An additional advantage of the oblique incision is that several mesenteric vascular arcades supply the suture line.

determined from the height and weight by use of a normogram and 1,200 ml. of fluids per square meter of body surface should be given daily. Overhydration leads to edema of suture lines, slows healing, and may temporarily obstruct the

Fig. 9.

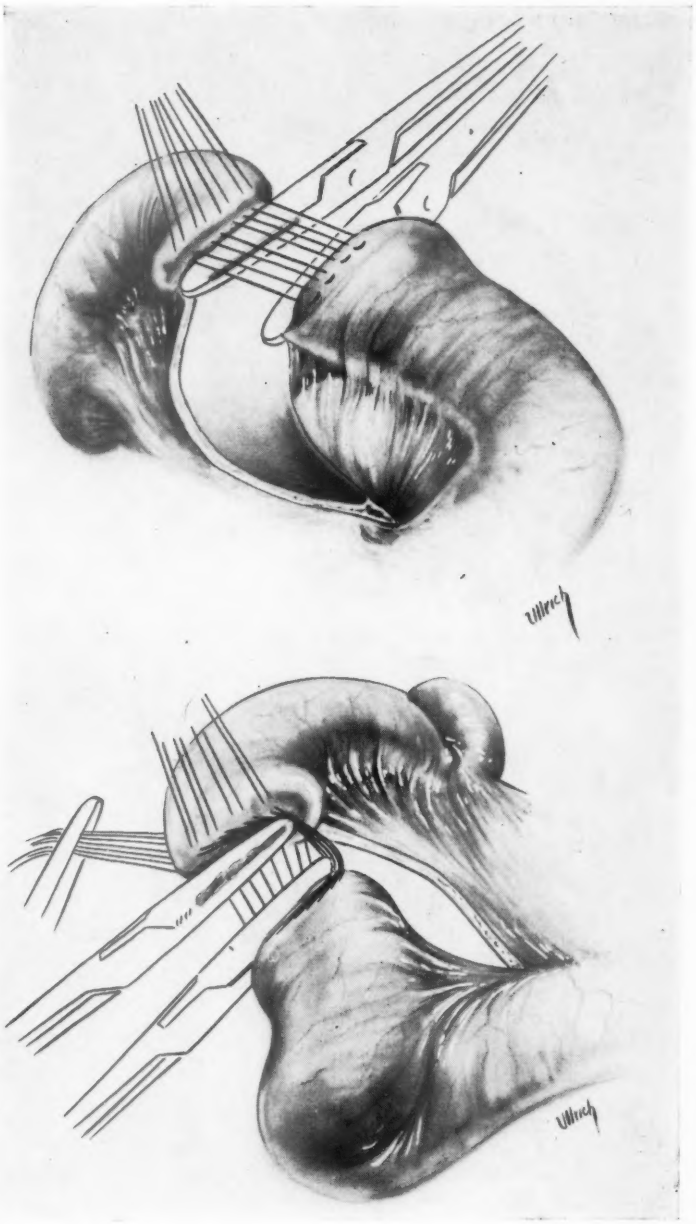

Fig. 10.

Fig. 9.—The clamps on the 2 ends of bowel are held parallel while the posterior row of Halsted sutures of No. 5-0 or No. 6-0 silk is placed. Care in placing the sutures permits them to be very close to the clamps while not entering the lumen of the bowel.

Fig. 10.—After the posterior row of sutures is completed, the clamps are rotated, and the anterior row of Halsted sutures is inserted into the muscular coats of the bowel wall. The sutures are hooked under the points of the clamps.

anastomosis. It may be necessary to keep the premature infant in an incubator to maintain body temperature. Oral feedings are begun when normal intestinal activity is established, which is usually 24 to 48 hours postoperatively. The child may be discharged in a week or 10 days if the wound is healed properly and he is gaining weight. The premature infant should remain in the hospital until he weighs over 5½ pounds.

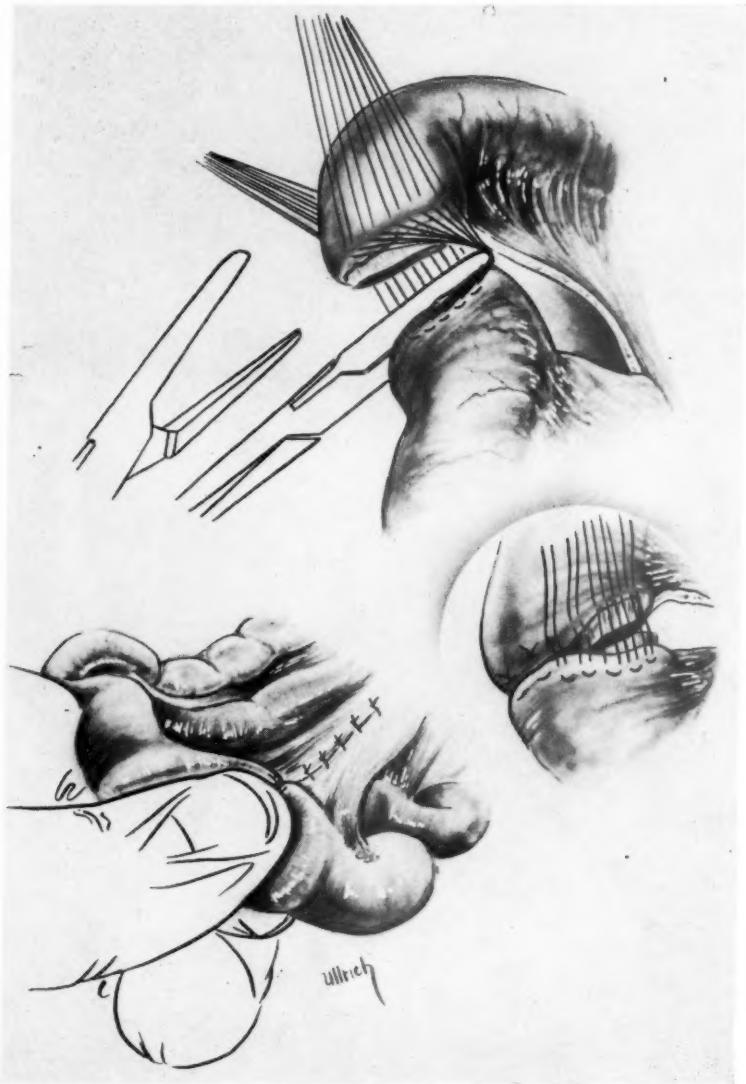

Fig. 11.

Fig. 12.

Fig. 13.

Fig. 11.—The clamps are removed without opening the sealed end of the bowel. Traction is then applied to the free ends of the sutures to withdraw the slack silk and pull the ends of the bowel into approximation.

Fig. 12.—The sutures are tied snugly enough to make the anastomosis watertight but not enough to crush or tear the bowel wall. The double mattress suture forms a fold of bowel wall on each side of the anastomosis that has a gasketlike effect and adds to the watertightness of the closure.

Fig. 13.—After the anastomosis is completed, the crushed ends of the bowel are opened by massaging the bowel between the thumb and forefinger. The defect in the mesentery is closed with interrupted suture, taking care to avoid blood supply.

RESULTS

During the 8 years from 1951 to 1959, 11 cases of small bowel atresia were managed by resection and primary end-to-end anastomosis (Table I). A twelfth patient had a jejunal diaphragm that was treated by resection of the mucosal diaphragm without resection of the bowel. The sex distribution was 10 boys and 2 girls. The age at the time of admission varied from 3 to 72 hours. Six of the patients were admitted at the age of 3 days. The body weight at birth varied from 4 pounds, 1 ounce to 9 pounds, 6 ounces, the average weight being 6 pounds, 2 ounces. The birth weight did have some prognostic significance since 2 of the 4 children weighing 5½ pounds or less did not survive. The smallest infant, weighing 4 pounds, 1 ounce, died. This was 1 of the 2 operative deaths. Four of the infants had other anomalies which complicated the management. Duplication of the ileum causing a cystic mass was found near the atresia in one patient. Another infant had a small omphalocele with the atretic bowel adherent to this area, and a major portion of the small bowel proximal to the ileal atresia had formed a volvulus about the attachment to the anterior abdominal wall causing multiple areas of infarction. Meconium peritonitis was a complication found in 1 case. Another child had an eventration of the duodenum, jejunum, ileum, and entire colon (except the sigmoid) through a ventral hernia. A barium enema was performed on 7 of the 12 infants before operation.

The site of atresia was single and found in the terminal ileum in 6 of the cases. In 4 patients the atresia was in the mid-small bowel and 2 others had multiple areas of atresia in the jejunum. Anastomosis was between the ileum and the colon in 2 patients, but in the remaining infants it was between 2 segments of small bowel, as described in a previous section. In the case of the jejunal diaphragm, the thin mucosal diaphragm was excised through an incision in the dilated jejunum proximal to the obstruction. General anesthesia was used with the 7 infants weighing over 5½ pounds. In 4 of the 5 smaller infants, local 0.5 per cent procaine was used.

The length of hospitalization varied from 8 to 38 days, the usual hospital stay being 9 to 12 days. Ten of the 12 infants had a satisfactory postoperative course and survived the operation. One infant died on the ninth postoperative day. Postmortem examination indicated a cardiorespiratory cause of death, for the anastomosis was intact. The infant was premature, weighing only 4 pounds, 1 ounce at birth, and had multiple areas of jejunal atresia which were resected at the time of operation. Postoperatively, the child failed to do well and had repeated episodes of apnea.

The other child had an ileal atresia with volvulus of the proximal dilated portion about the attachment to an omphalocele. An end-to-end anastomosis was accomplished after resection of 15 cm. of the proximal dilated ileum. On the fourth postoperative day a perforation of the ileum developed proximal to the anastomosis apparently on the basis of impaired blood supply from the volvulus.

TABLE I. CONSECUTIVE CASES, 1951 TO 1959

	PATIENT	WEIGHT (POUNDS)	AGE (DAYS)	OTHER ANOMALIES	BARIUM ENEMA	ATRESIA	HOSPITAL STAY (DAYS)	RESULT
1.	B. G.	7 8/16	1	—	0	Mid-small bowel	10	Good
2.	B. B.	6	3	—	0	Terminal ileum	9	Good
3.	H. C.	6	3	Duplication	0	Terminal ileum	16	Good
4.	M. McG.	5 8/16	1½	Omphalocele; volvulus	+	Terminal ileum	34	Died
5.	E. B.	5	3	—	+	Terminal ileum	12	Good
6.	D. F.	5 7/16	2	—	+	Terminal ileum	10	Good
7.	T. K.	4 1/16	3	—	0	Jejunum, multiple	9	Died
8.	R. P.	5	3	Meconium peritonitis	+	Terminal ileum	8	Good
9.	K. B.	6	2	—	+	Jejunum, multiple	38	Good
10.	R. H.	9 6/16	3	—	+	Mid-small bowel	10	Good
11.	B. D.	6 3/16	3 hours	Eventration	0	Jejunum	14	Good
12.	D. O.	8 7/16	1	—	+	Jejunal diaphragm	9	Good

Although an ileostomy was performed, the child's condition deteriorated progressively and he died on the thirty-fourth postoperative day with inanition and severe exfoliative dermatitis.

Only the patients in this series with severe, hopeless anomalies died. The premature infant had multiple atretic areas requiring excision of a major portion of the intestine and would have presented a problem in nutrition if he had survived. The second infant had multiple anomalies including an omphalocele and volvulus with impairment of the blood supply to a large area of the intestine.

A follow-up evaluation has been obtained on the 10 surviving patients. Information has been sent by letter from the parents or local physicians. The length of time following operation varied from 1 to 8 years. No further operations were necessary after the primary anastomosis. The children gained weight and had a normal development when the atresia was managed as previously outlined.

Several embryologic explanations for the anomaly of intestinal atresia have been suggested. During the sixth and seventh weeks of fetal development the intestine is a solid tube. The lumen is gradually opened by coalescence of the vacuoles. Failure of the vacuoles to restore the lumen completely may lead to atresia.[8] This suggestion is more logical in explaining the findings in duodenal obstruction where there is no loss of continuity of the bowel wall than it is in jejunal and ileal atresia where the 2 ends may be completely separated.

A second embryologic explanation for this anomaly involves the occurrence of local mesenteric thrombosis with a small segment of the intestine undergoing aseptic necrosis in utero. A break in the continuity of the intestinal tract is thus established.[6] Experimental data with fetal dogs has been collected to support this hypothesis.[1]

A third hypothesis has been offered.[12] As the intestine is withdrawn into the abdominal cavity from the herniation into the umbilical cord, it is suggested that a loop of small bowel may be caught in the closing umbilical ring with resultant aseptic necrosis of this loop. The fourth case in this series lends support to this theory.

Recently a fine study has been made by Louw and Barnard[11] elucidating the etiology of this condition. They performed operations on fetal puppies, and were successful in producing small bowel atresia. Several anatomic variations were regularly obtained by ligating a number of vascular arcades, by twisting a loop of intestine to simulate a volvulus, and by the intussusception of a segment of bowel. Thus, the mechanism of fetal intussusception and other intrauterine accidents have been designated as causes of small bowel atresia.

The necessity for the resection of the bulbous, dilated, proximal end of the atretic bowel is now generally recognized. Support of this maneuver was recently added by laboratory experiments.[12] It was found that once a segment of intestine became chronically dilated, this dilatation failed to return to normal after the obstruction was relieved. Impaired peristaltic activity in this segment also persisted.

In our experience the operation of resection and primary aseptic anastomosis has been relatively safe and followed by an uncomplicated postoperative course.

In contrast to this experience, 3 patients were referred with ileal atresia who had ileostomies performed elsewhere and were particularly difficult to manage.

The first child was a boy referred at 1 month of age because of malfunctioning ileostomy. At birth he weighed 7 pounds, 10 ounces and had an ileostomy performed for ileal atresia. Initially he did well and regained his birth weight but then his condition deteriorated and his weight went down to 5 pounds. After preparation, the ileostomy was resected and an ileocolostomy was performed following which the child gradually regained his health.

The second patient was a female child who was referred at the age of 5 weeks with an ileostomy and wound dehiscence, a severe problem in malnutrition resulting from an ileal atresia. She was in the hospital for 1 month before the wound finally healed and she started to gain weight. A resection of the ileostomy with an end-to-end anastomosis was necessary before she finally maintained a persistent gain in weight.

The third patient was a boy referred at the age of 2 months because of a malfunctioning ileostomy. Birth weight was 6 pounds, 11 ounces, but during the 2 months after operation he lost weight to 4 pounds, 11 ounces. Following resection of the ileostomy and an end-to-end ileocolostomy, he had no further difficulty.

Experiences such as these suggest that resection and primary end-to-end anastomosis present fewer problems in the postoperative course.

The history of successful management of small bowel atresia goes back several decades to 1911 when Fockens was the first to report the survival of a patient with this condition.[7] Snyder and associates reviewed the world literature in 1950 and found 20 successfully treated cases to which they added 5 of their own.[14] In 1951, Baronofsky described the single layer, end-to-end anastomosis in connection with the report of the survival of a premature infant with ileal atresia.[2] However, he rotated the clamps so that the mesenteric border of the proximal end was sutured to the antimesenteric side of the distal end. Clawson reviewed the complications of side-to-side intestinal anastomosis and labeled this a physiologically unsound procedure.[5] The late complications of ulceration, dilatation, and anemia were troublesome as the blind proximal end enlarged into a dumbbell-shaped sac.

In 1953, Gross reviewed the results in the management of jejunal and ileal atresia at the Boston Children's Hospital.[10] The preferred operation was an ileostomy with later crushing of the spur and extraperitoneal closure. Fourteen of 20 patients survived the operation. Benson reported a personal series of 10 patients with atresia of the small intestine before the American Surgical Association in 1955.[3] Eight patients survived resection and primary anastomosis (end-to-end, side-to-side, or end-to-side). Gerrish reported before the same Association meeting 7 survivals in 10 patients with atresia managed by open, two-layer anastomosis without resection.[9] He recommended proximal tube enterostomy to decompress the dilated loop postoperatively.

In 1955, Nixon reviewed the results in the management of 27 cases of jejunal and ileal atresia at the Hospital for Sick Children in London.[12] Only 33 per cent survived direct anastomosis of the blind ends. However, 67 per

cent recovered when a resection and "end-to-back" anastomosis were performed. The experience at the Babies' Hospital in New York City was reported by Santulli in 1956.[13] Eight of 26 infants survived various types of procedure, but an enterostomy was preferred. Clatworthy and Lloyd reviewed 163 patients with neonatal intestinal obstruction at the Ohio State University Children's Hospital, including 20 infants with jejunal and ileal atresia. The over-all mortality in the group with intestinal atresia was 46 per cent.[4] The preferred method of management had turned from the three-stage Mikulicz procedure to resection and end-to-end anastomosis.

This variety of opinions, based on a wide experience in the field, suggests that the management of small bowel atresia remains a challenge to the surgeon dealing with intestinal obstruction of the newborn. However, the extremely high mortality of several decades ago has been reduced to reasonable levels by early diagnosis and operation, careful management of anesthesia, judicious use of intravenous fluids and blood transfusions, antibiotics, and gastrointestinal suction.

SUMMARY

A study of 12 consecutive cases of small bowel atresia is reported. Details of management with resection and primary end-to-end anastomosis as the preferred procedure are described. This method of treatment is recommended since the mortality rate is so low and the postoperative course is relatively uncomplicated.

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PSEUDOCYSTS OF THE PANCREAS IN INFANTS AND YOUNG CHILDREN

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PSEUDOCYSTS of the pancreas in the pediatric age group have received little attention in either general or specialized medical literature. The scarcity of reported cases in infants and young children tends to minimize or actually to eliminate consideration of this possibility in the differential diagnosis of abdominal masses in children. Failure to include this lesion among diagnostic probabilities may have tragic consequences, as one of our cases will illustrate. It is likely that almost any medical center or any surgeon with a reasonably large practice in pediatric surgery could discover one or more cases if his files were searched. If adequate attention were focused on more of these surgically curable cases, pancreatic pseudocyst as a pediatric disorder might be given the recognition and diagnostic consideration that it properly deserves.

In his report of a single case in 1951, Mithoefer[16] had difficulty finding other conclusively proved cases of pancreatic pseudocysts in young children. He cited references to 6 case reports, accepting those of Drennen[4] and of McWhorter[13] as true pseudocysts. Drennen's case (1922) was that of a 4-year-old Negro boy, injured by a wagon, who recovered after external drainage of the cyst. McWhorter (1925) compiled and tabulated 19 cases of pancreatic cyst from various causes, that had been attended by members of the Chicago Surgical Society. Four of these resulted from trauma. One of these occurred in a 6-year-old boy, a patient of H. Richter, who recovered after external drainage. The other patients in McWhorter's series were adults. Mithoefer concluded that all other childhood cases prior to his initial report "were certainly not pseudocysts" and considered his case, in a 20-month-old girl, to be the third authentic one published.

We have reviewed the original reports of the other 4 cases cited by Mithoefer and although the data given are meager by present standards, we believe that Connolly's case[2] (1911) and that of Telling and Dobson[21] (1909) might be construed as having been pseudocysts, even though there are valid objections to this interpretation. The cases of Railton[19] (1896) and Eha[5] (1922) are clearly examples of true congenital or developmental epithelium lined pancreatic cysts, as is that of Miles,[15] reported last year. Very recently, Covington[3] reported 2 additional cases of pseudocyst and found 2 more in the literature[10, 12] between Mithoefer's report and his own, bringing the total

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of unquestioned cases to 7. Both of Covington's cases occurred in children 8 years old or younger, as did all 3 of ours. He apparently overlooked another case in a 6-year-old girl reported by Blumenstock, Mithoefer, and Santulli[1] in 1957.

In recording 3 additional cases,* our purpose is not to emphasize the extreme rarity of pancreatic pseudocysts in young children. We would suggest, rather, that while they may be unusual in this age group, they probably are not actually rare and if the collective experience of all who have seen such cases could be assembled, there would be a significant number of them. Our cases are presented in enough detail to establish their authenticity.

CASE REPORTS

CASE 1.—P. C., a white male infant, 1 year old, was admitted to the Boston City Hospital July 5, 1942, with abdominal enlargement said to have been present for 3 weeks, and with an unremarkable antecedent history. His parents were 30 years of age, his birth weight was 7 pounds, and his delivery, neonatal course, and subsequent growth and development had been normal. His weight upon admission was 25 pounds. It was stated that 6 days before admission he had suffered transitory diarrhea with 8 stools a day but no vomiting.

Examination showed a well-developed, well-nourished child, acutely ill but not febrile. The temperature was 99.0° F., pulse 100, and respiration 36. The abdomen was severely distended and displayed a definite fluid wave, but there was no evident tenderness and no solid masses could be felt. The white blood cell count was 9,000, with 45 per cent neutrophils. Hemoglobin was 9.5 Gm. when the child was admitted and it had dropped to 6.0 Gm. by the twelfth day of hospitalization. Results of stool and urine examinations were entirely within normal limits, a blood culture was sterile, and the fasting blood sugar was 76 mg. per 100 c.c. Plain x-ray films of the abdomen showed ascites and a normal intestinal gas pattern.

On the second day of hospitalization abdominal paracentesis yielded 600 c.c. of serosanguineous fluid and on the sixth day another 700 c.c. of bloody fluid was obtained by the same route. Chemical analysis of the fluid was not made, but centrifuged cell blocks from both specimens showed elements suspected of having malignant characteristics. Without further study a diagnosis of generalized carcinomatosis was made and roentgen therapy was begun on the ninth day. The child's temperature rose to 101.4° F., he began to vomit sporadically, and his condition deteriorated swiftly. He died on the fourteenth day.

An autopsy was performed 2 hours post mortem. It disclosed a firm, encysted mass measuring 8 by 10 cm. in the body of the pancreas, partly filled with dark red fluid. It was connected with the peritoneal cavity near the inferior surface of the liver by a narrow, fistulous tract passing behind the second portion of the duodenum. Serial gross sections through the rest of the pancreas showed no abnormalities and the duct system was intact. The cyst wall showed no lining membrane, and the final diagnosis was hemorrhagic cyst of the pancreas, with a sinus tract communicating with the peritoneal cavity. No evidence of malignant tumor was found, and the remainder of the autopsy was unremarkable.

CASE 2.—M. C., an 8-year-old white girl was struck in the pit of the stomach by the handle bar of her bicycle when it collided with an automobile. She was admitted to the hospital for observation because of abdominal pain but this subsided so rapidly that she was discharged after 36 hours. She was readmitted 12 hours later, on July 13, 1954, with severe epigastric pain. Examination at this time showed pronounced epigastric tenderness and muscle spasm, and absent peristaltic sounds. A delayed rupture of the spleen was

*Cases 1 and 2 are from the files of the Boston City Hospital. Case 3 was attended by one of us (C. M. L.) in another city.

believed to be present but upon laparotomy a retroperitoneal hematoma was found, dissecting into the transverse mesocolon, the lesser omental bursa, and around the pancreas. A drain was placed in the lesser sac and the abdomen was closed.

On the fourth postoperative day the drain was accidentally removed. Three days after this the child complained of abdominal pain again and epigastric fullness was observed. The drain was reinserted through the original incision and for 2 weeks thereafter pancreatic fluid, identified by tests for tryptic activity, drained from it. The epigastric fullness did not recede, however, and a mass became distinctly palpable. Roentgenographic studies showed the stomach to be pushed forward by a retrogastric mass which, in successive clinical observations, slowly increased in size.

The white blood cell count rose to 10,000 and the serum amylase was 1,600 units. Urinary diastase was 1,285 units. The blood sedimentation rate was 60 mm. per hour and the fasting blood sugar 97 mg. per 100 c.c. A trypsin test of the stool was positive.

A second laparotomy was performed on Sept. 2, 1954, and a 20 by 25 cm. pseudocyst of the pancreas was found. It was treated by marsupialization. The contained fluid was sterile on culture and its pH was 7.5, but no other chemical analysis was made. Drainage continued for a week and then ceased quite abruptly. The serum amylase level dropped to 600 units. The tract closed spontaneously and the child was discharged on the twelfth postoperative day, free of symptoms. She has remained well for 5 years since then, the last report having been made in November, 1959.

CASE 3.—H. I., a boy 4 years, 4 months of age, born Oct. 13, 1949, was the third of his parents' six children. All of his siblings were living and well. He was admitted to the Children's Hospital of Cincinnati, Feb. 8, 1954. His parents stated that, although vigorous and active, he had always been considered "puny," and not as strong as the other children.

In January, 1953, about 12½ months before admission, he had contracted mumps along with all of the other children in the family, but did not make as rapid a recovery. Soon after he was believed to have recovered, the parents noted a gradual enlargement of the abdomen but since it gave the child no discomfort and was not strikingly evident when he was clothed, they took no steps to have it investigated. The child's appetite, never very robust, remained fairly good and he seemed normally active and playful. About 2 weeks prior to his admission the abdominal enlargement began to increase rather rapidly. The child complained of vague, nonlocalized abdominal pain and slowly increasing shortness of breath. After radiological studies had suggested the possibility of pancreatic cyst, both the child and his parents were closely questioned about abdominal trauma and all denied that any had occurred. The father said that the children did "play pretty rough" but insisted that there had been no known trauma severe enough to make him stop playing or lie down. The child, within the limits of a 4-year-old's memory and vocabulary, was sure that he had sustained no abdominal trauma at any time.

There was no history of jaundice, either during infancy or later. Bowel movements had remained regular, and even after acceleration of the abdominal swelling the boy had continued to eat almost as usual. His pain was evidently not severe, and his principal inconveniences were the weight of his abdomen and shortness of breath.

On examination the vital signs were found to be essentially normal except for a slightly increased respiratory rate. Temperature was 98.4, pulse 84, respiration 28, blood pressure 95/50, and weight 33¼ pounds.

The child was pale, appeared chronically ill, and was small for his age. General examination disclosed nothing remarkable, however, except for a strikingly protuberant abdomen (Fig. 1) in which a large cystic mass could be felt, filling the right side. The liver margin could not be distinguished from this mass. Although the mass seemed to extend into the pelvis, rectal examination was negative. Peristaltic sounds were normal in the left abdomen. The results of laboratory studies are recorded in Table I.

Radiographic contrast studies included excretory pyelograms, barium enema, and an upper gastrointestinal series. The pyelogram was normal except for slight pyelectasis

TABLE I. RESULTS OF LABORATORY STUDIES

Hemoglobin	10.4 Gm.	Bilirubin	
White blood cells	8,750	Total	0.4
Neutrophils	76%	Direct	0.2
Platelets	Sufficient	Cephalin flocculation	Negative
Urine	Negative	Total lipids	495 mg./100 c.c.
Nonprotein nitrogen	25 mg./100 c.c.	Co_2 T	21 minutes

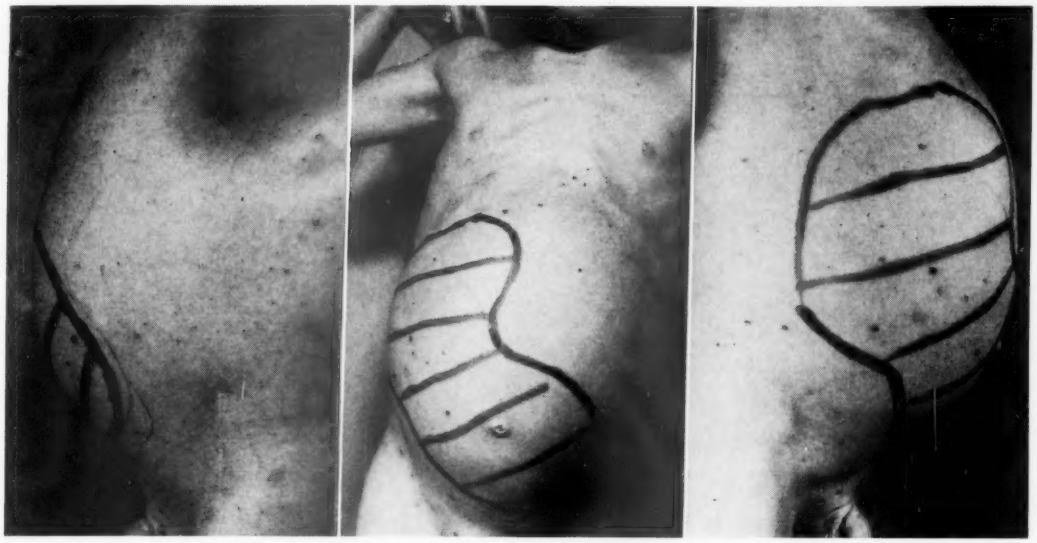


Fig. 1.—Photographs of the abdominal protrusion presenting on admission to the hospital, in Case 3.

and ureterectasis on the right. Neither kidney was displaced. The gastrointestinal series showed both the stomach and the duodenum to be pushed cephalad, and the ascending and transverse colon toward the left. The preoperative diagnoses were, in order of preference, pancreatic cyst, choledochus cyst, and embryonal sarcoma of the liver.

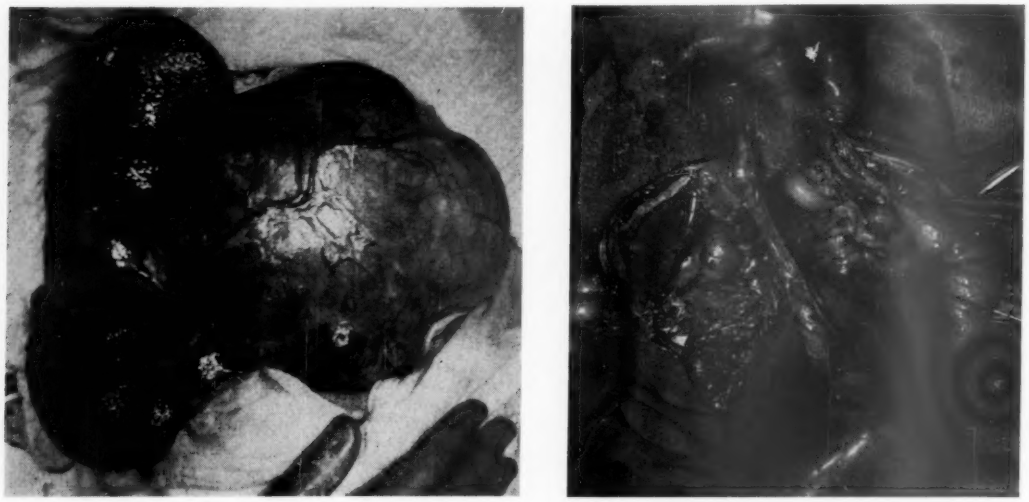
An operation was performed through a transverse upper abdominal incision on Feb. 12, 1954. A large trilocular cyst was found (Fig. 2*A*), the central component of which was covered by stretched transverse mesocolon and omentum. The right lateral component was covered with an apparent pseudoserous membrane and contained greenish-brown fluid which partially clotted when a sample was aspirated and set aside in a glass container. A third loculation, above the second (not visible in the photograph), contained similar fluid. The thick-walled central cyst contained thick, dark, greenish-black fluid which did not clot on standing. The 2 thin-walled cysts were easily dissected out and removed. The thick-walled cyst was found to lie between the posterior layer of the omental bursa and transverse mesocolon, bulging into the greater omental sac. It was possible to dissect it out, leaving the middle colic vessels undamaged. The duodenum had been pushed upward, narrowing the gastroduodenal loop rather than widening it, and the cyst was dissected from it quite easily. Fig. 2*B* shows the rent in the transverse mesocolon and the remains of the ligament of Treitz after all three components of the cyst had been completely removed. Final attachment was to the head of the pancreas, but the duct was undamaged. The external biliary tract was entirely normal.

The wound was closed without drainage, and the child made an uneventful recovery. He was discharged from the hospital on the seventh postoperative day.

Chemical analysis of samples of the fluid in the 2 larger cysts yielded the results shown in Table II.

The detailed description of the gross and microscopic appearance of the cyst, by Dr. B. H. Landing, is omitted for brevity. His diagnosis was pseudocyst of the pancreas.

The child has remained well since he left the hospital, his last follow-up visit having been April 8, 1959. Fig. 3 is a photograph taken in October, 1954, 8 months after the operation.



A. *B.*

Fig. 2*A*.—Photograph of the pancreatic pseudocyst in Case 3 as it appeared when first delivered through the laparotomy wound. A smaller third loculus was present above the dark mass on the patient's right, but is not visible in the photograph.

Fig. 2*B*.—Appearance of the upper abdominal viscera after the entire pseudocyst had been excised. The remnant of the ligament of Treitz is held between the operator's fingers.

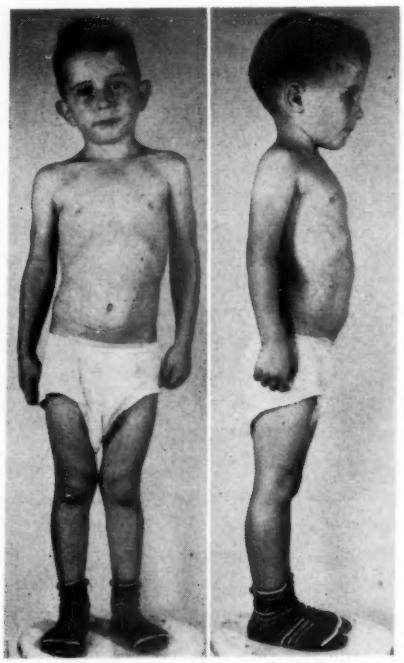


Fig. 3.—Photograph of the patient (Case 3) taken 8 months after operation.

TABLE II

	THIN CYST; LIGHT FLUID	THICK CYST; DARK FLUID
Bilirubin prompt	0.1	0
Bilirubin total	1.5	2.1
Amylase	160 units	94 units
Chloride	115 mEq./1	117 mEq./1

COMMENT

In reports of fairly extensive experience with pancreatic cysts in adults, an occasional case encountered in older children and adolescents is included. In Meyer, Sheridan, and Murphy's series of 31 cases,[14] only 2 occurred in patients under the age of 20, the youngest being 14 years old. Judd[7] reported 41 cases from the Mayo Clinic in 1926 and, with Mattson and Mahorner,[8] added 47 more in 1931. All of their patients were more than 20 years old. Shore[20] has recently added 1 well-substantiated case in a 13-year-old boy.

The direct relationship between blunt abdominal trauma and the development of pancreatic pseudocysts has been recognized for many years and was strongly emphasized by Lloyd[11] in 1892. More recent authorities on the disease as it occurs in adults differ as to the relative incidence of trauma and of spontaneous acute pancreatitis. Estimates of the number of cases caused by acute pancreatitis range from 1 or 2 per cent to more than 50 per cent, with most of the other cases being attributed to trauma. In some, Lussky's case, for example, no obvious cause is recognized.

Acute hemorrhagic or necrotizing pancreatitis is predominantly a disease of adults but it is not unknown in children. Blumenstock, Mithoefer, and Santulli reported 4 cases in 1957, in 3 infants aged 8, 13, and 15 months respectively, and in a 6-year-old girl. The last child developed a pseudocyst requiring marsupialization and is one of those referred to in our introductory remarks. These authors found 36 other cases of acute pancreatitis in children, reported between 1927 and 1957, but all of these patients were 13 or more years old. The cause of this form of pancreatitis in childhood remains obscure and associated biliary tract disease is apparently distinctly uncommon. Intestinal parasites invading the pancreatic ducts have been credited with producing pancreatitis in 7 cases but, according to the above authors, conclusive proof was offered in only one of these.

The common form of pancreatitis encountered in children is that which occurs as a complication of mumps. It is diagnosed clinically by abdominal pain, tenderness, and nausea in the presence of, or following, epidemic parotitis. In 1922, Farnam[6] reviewed the literature on mumps pancreatitis in connection with her report of a single unusual case. She collected 119 cases from the literature and considered 73 of these well documented enough to warrant tabulation and arrangement in a graphic comparison study. Of the entire group of 119 cases, 31 were said to have occurred "in children" but exact ages were not stated in so many that an accurate calculated percentage is not possible. Farnam's own case occurred in a 28-year-old male, whose severe pancreatitis developed 5 days after recognition of mumps and who underwent a laparotomy 9 days later. He recovered after more than 2 months in the hospital.

Neither severe pancreatitis nor pseudocyst would appear to be very common as a complication of mumps. The usual case of mumps pancreatitis produces only mild to moderately severe abdominal symptoms, and benign recovery is the rule. Zellman is quoted by Blumenstock and co-workers as having encountered it in 15 per cent of 600 cases of mumps.

The confusing fact is that the serum amylase levels were elevated in 75 per cent of these 600 cases and abdominal symptoms were prominent in only 15 per cent. The evaluation of mumps pancreatitis in relation to pseudocysts of the pancreas is obviously difficult in the light of these observations, yet our Case 3 should be mentioned, even though a direct etiological relationship is necessarily speculative. Where trauma is the accepted causative factor in adults, the time interval between injury and the recognition of the pancreatic pseudocyst may range from 24 hours to 4 years[14] and Farnam found that the interval between mumps and pancreatitis ranged from 4 days to 8 weeks. Thus the 12½ month interval between the mumps and the pancreatic cyst does not exclude a possible relationship in our case. The parents of this child were quite explicit in stating that gradual abdominal enlargement began soon after the boy's slower than usual recovery from mumps. The thick-walled component observed at operation might well have been developing during this period, and the sudden exacerbation in the last 2 weeks may have resulted from a hemorrhage into its wall, producing the two thin-walled collateral chambers. We believe that mumps pancreatitis may reasonably be postulated as a possible etiological factor in some cases of pancreatic pseudocyst.

Antecedent trauma is clearly established in the cases of Drennen, McWhorter, Mithoefer (first case), and Levitsky and his colleagues. It was also present in Shore's case, both of Covington's cases, in 1 of our 3, and presumably in some others less explicitly described. Since the relationship is well accepted in adults we have no reason to contest it as the probable more common cause in childhood. Considering the increasing vehicular traffic hazards of today, we feel sure that many cases have occurred that have not been reported and that the total number of cases, whether reported or not, is likely to increase.

When the time interval between trauma and the development of the cyst as a palpable mass is short, and especially when an elevated serum amylase is observed, the diagnosis of pancreatic cyst should be suspected. When, in addition, the characteristic visceral displacements of a retroperitoneal mass are demonstrated by barium contrast studies, a definitive preoperative diagnosis is virtually inescapable.

If the development of the cyst is slow, an elevated serum amylase is less likely to be present, subjective symptoms may be minimal, and differentiation between pseudocyst and splenomegaly, choledochus cyst, mesenteric cysts, or congenital duplications of the bowel (to mention a few nonneoplastic lesions) may be more difficult. The worst possible diagnostic error is to assume that the lesion is malignant (Case 1) and to treat it by radiation without a conclusive pretreatment diagnosis. The error here recorded occurred 18 years ago

and such a mistake would be much less likely to be made today, but the importance of a definitive histologic diagnosis, by means of a laparotomy and biopsy, in all cases of abdominal neoplasm, whether operable or not, cannot be overemphasized.[9] If such a rule were conscientiously followed, errors of this kind could be entirely eliminated.

Barium contrast studies may be extremely helpful, and when the characteristic widening of the gastroduodenal loop is demonstrated (so familiar to those who have seen it in adult cases), the diagnosis is not difficult. But since the expanding pseudocyst may dissect along any of several alternative planes, the range of possible roentgenographic patterns is extensive. In our Case 3, both the stomach and the duodenum were deflected upward, producing a narrowed rather than a widened gastroduodenal loop, and the lateral components of the cyst extruded through the peritoneal folds around the ligament of Treitz (Figs. 2*B* and 4).

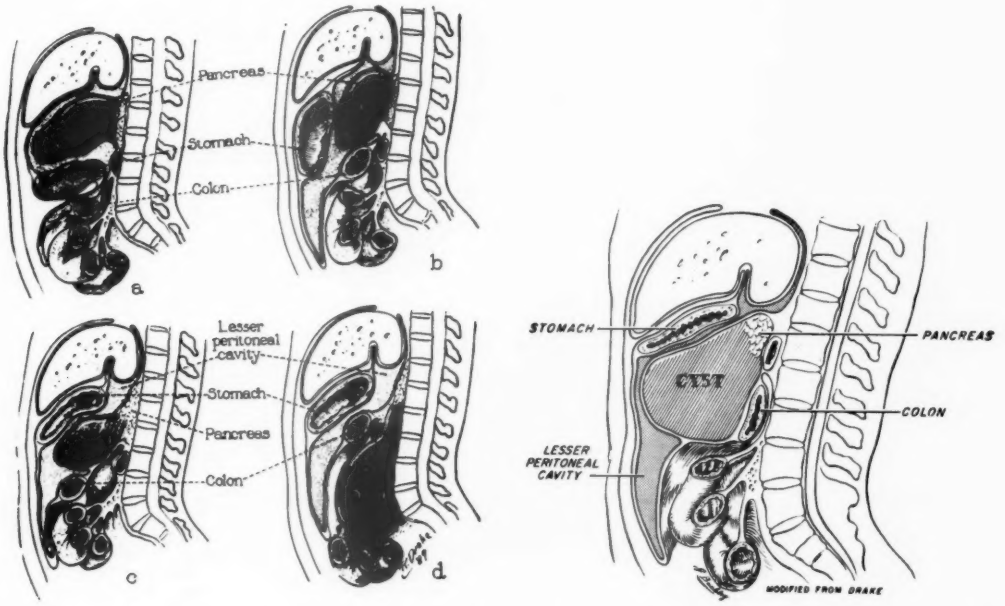


Fig. 4.—Schematic drawings of various planes of dissection along which pseudocysts of the pancreas may expand. The drawings on the left, *a-d* inclusive, are reproduced from the article by Judd, Mattson, and Mahorner.[8*] Our Case 1 conformed approximately to the drawing designated *b*, and Case 2 to the one labeled *c*. The drawing on the right (adapted from those of Judd and his associates) illustrates, within the limitations of a single sagittal section, the situation in our Case 3. The narrowed gastroduodenal loop is difficult to diagram in a single projection.

*Reproduction of drawings *a*, *b*, *c*, and *d* is with written permission of the Section of Publications, The Mayo Clinic, and of the *A. M. A. Archives of Surgery*.

With respect to the surgical management of pancreatic pseudocysts in children, the choice of procedures is essentially the same as in adults: external drainage by marsupialization, internal drainage into some portion of the upper gastroenteric tract (whether it be directly into the stomach or by means of a Roux-en-Y anastomosis into the jejunum), or complete single stage excision. We believe that the fragile serosal membranes of young children facilitate complete excision, even of fairly large cysts (Levitsky,[10] Lussky,[12] and our

Case 3), if dissection is carefully conducted. It has the advantage of leading to rapid convalescence, as evidenced by the fact that our patient left the hospital with a healed wound on the seventh postoperative day. However, the risk of peritoneal contamination with enzymatically active cyst contents is one to be avoided, and when the cyst is multilocular or too thin walled to permit a strongly constructed internal drainage stoma to be made, there is no question that marsupialization is the safest procedure. Its principal disadvantage is that drainage is sometimes quite protracted. The judgment and experience of the surgeon must be the deciding factor in each individual case.

SUMMARY

Three cases of pancreatic pseudocyst in children 8 years old or younger have been reported, bringing the total that we can find in the literature to 11. One of the cases previously recorded was mistaken for an advanced abdominal malignancy, resulting in unsuccessful treatment and a fatal outcome.

Consideration is given to a possible causal relationship between the pancreatitis of mumps and some cases of pancreatic pseudocyst in young children. Spontaneous nonspecific pancreatitis also occurs occasionally in this age group, and may result in pseudocyst formation. The usual cause of this lesion in childhood is blunt abdominal trauma. There is little doubt that many unreported cases occur, and that the incidence will increase with the rising rate of vehicular traffic accidents and other sources of abdominal injury, even in relatively young children.

We believe that pancreatic pseudocysts are not actually very uncommon as a childhood disorder and that they should occupy a more prominent place than they presently do in the diagnostic consideration of abdominal masses in pediatric practice.

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

ACHALASIA OF THE ESOPHAGUS

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TO a very large extent, the now classical paper by Barrett and Franklin,[9] in the *British Journal of Surgery,* published in 1949, awakened British and American surgeons to the danger of esophagitis in the anastomotic operations for achalasia, and revived the operation which Ernst Heller[57] had described in 1914. It has puzzled us that a sound procedure should have been apparently discarded for 35 years, and it seemed of interest to trace the history of this operation and the reasons for its temporary eclipse.

HISTORY OF THE DISCOVERY OF ACHALASIA

Achalasia of the esophagus has been a known entity for almost 300 years, although it appears that sustained interest in the disease and general recognition date from the latter part of the nineteeth century, when Zenker and von Ziemssen collected 18 cases (including one of their own) of dilatation of the esophagus ("Erweiterungen der Speiseröhre"), and 4 cases of what they called "Stenosis Esophagi."

The development of better and more accurate diagnostic methods, roentgenography, fluoroscopy, and esophagoscopy, combined with a well-defined therapeutic approach, operative or nonoperative, removed the disease from the sphere of the pathologist and revived the interest of the clinician.

Thomas Willis[175] of Oxford is generally credited[67, 92, 93] with the first description of achalasia. In his book, *Pharmaceutice rationalis,* or, *An Exercitation of the Operations of Medicines in Humane Bodies,* Willis describes a case "of a certain man of Oxford" who had "an almost perpetual vomiting to be stirred up by the shutting up of the left orifice. He was wont, very often, though not always, presently to cast up whatsoever he had eaten. When that

This paper had its inception in the interest of two of us, M. M. R. and F. M. S., in the reasons for the temporary eclipse of the Heller procedure. In the attempt to obtain a photograph of Dr. Heller we wrote his former associate, Dr. H. Ubermuth in Leipzig. To our delight the letter was forwarded and promptly answered by Dr. Heller himself from Leipzig where he is now well and active at the age of 82. A lively correspondence ensued, and Dr. Heller joined us as coauthor. The final section on the evolution of his procedure was written largely by Dr. Heller.

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no medicines could help and he languished away for hunger, and every day was in danger of death, I (Willis) prepared an instrument for him like a Rod, of a whale bone, with a little round button of sponge fixed to the top of it. By this means he hath daily taken his sustenance for 15 years and doth yet use the same machine, and is yet alive and well."

Some 60 years later, in 1733, Frederic Hoffman[66] of Halle, Germany, presented his *Dissertatio Inauguralis Medica de Spasmis Gulae Inferioris et de Nausea.* From the symptoms and findings described, it can safely be concluded that he meant what is known today as achalasia. In a very colorful report he states that "the spasm of the esophagus is characterized by a sensation of pressure in the back and below both shoulders, and that the patient is incapable of swallowing cold beer, whereas he is able to take warm drinks." Hoffman wrote that mechanical obstructions do not give these symptoms. In another case, symptoms occurred suddenly at night and regressed spontaneously, but recurred with the swallowing of a hot drink. He concluded, in this case, that "cum frigida tum calodiora spasmis nocent." Some of the etiological factors found in Hoffman's script are "exuberant love, unnatural desires," whereas convulsions predispose to the spasm, and emotional upset prevents the food from passing into the stomach. Hoffman appreciated the role which is played in this disease by the personality and added that the condition is found mostly in hypochondriacal males and hysterical women.

In 1821, Purton[122] in England, described "an extraordinary case of distention of the esophagus, forming a sac, extending from two inches below the pharynx to the cardiac orifice of the stomach." He goes on, "The present case, however, of more than 20 years standing, I believe to differ from any one yet recorded." When a youth, the patient received a severe blow upon the sternum. During the entire duration of his disease he had episodes lasting 3 weeks or more during which he would be unable to swallow any food satisfactorily. "An attack would often be induced by irritation of mind, or by constipated state of bowel." The patient expired at the age of 43 of inanition, and at autopsy "the esophagus was found to be greatly distended, forming a sac: It contained by admeasurements full two quarts. The cardiac orifice was found pervious, but much contracted." Sir Astley Paston Cooper had seen the patient and recommended the use of bougies, "but from the difficulty of introducing them, and the great pain and irritation consequent upon their use, they were laid aside." Purton presented the Museum of the Royal College of Surgeons with the preparation of the stomach and esophagus.

Herbert Mayo,[97] of London, in 1828 described a case in which death followed exhaustion, after 10 years of symptoms. The autopsy of that patient revealed an esophagus gradually enlarging from the pharynx and 4 inches in diameter above the cardia, the latter being of normal caliber. In 1833, Hannay[50] added another case in the *Edinburgh Medical and Surgical Journal.* In this patient, too, the difficulty of swallowing had existed since boyhood, at which time he had received a violent blow on the chest, inflicted by a club or shinty. The author recommended temperance, but the patient went on eating and living

irregularly and copiously, and was found dead one morning "after a night of hearty eating and drinking." At postmortem the esophagus was found dilated and distended with "ingesta." The examination of the brain revealed an "apoplexy" to have been the cause of death. In 1842, von Rokitansky[165] described a case in his *Handbuch der pathologischen Anatomie* in which the esophagus "could hold a man's arm." This specimen was placed in the Pathological Museum at Vienna.

In 1866, Samuel Wilks[174] of Guy's Hospital (who, with Moxon, determined ulcerative colitis to be a distinct disease) showed a specimen before the Pathological Society of London, from a man 74 years old, who had died of pneumonia. This patient had suffered with difficulty in swallowing all his life, and had been treated by the father of a Dr. Rootes since 1812. Dr. Rootes came to know the patient and cared for him in 1831. Sir Astley Cooper had seen the patient 40 years before his death, and had passed a bougie without any difficulty. In 1874, Zenker and von Ziemssen[181] were able to collect 18 cases of "dilatation of the esophagus" in the world literature and recorded the names of the authors in the chapter on "Krankheiten des Oesophagus" in *Ziemssen's Handbuch der Speciellen Pathologie und Therapie* (Purton, Hannay, von Rokitansky [2 cases], delle Chiage, Abercrombie, Oppolzer, Spengler, Wilks, Giesse [2 cases], Ogle, von Luschka, Klebs, Davy, Stern, Dave, and Zenker). In the same work there is a chapter called "Simple Stenoses of the Lower Oesophagus." From the macroscopic picture described, as well as from the cases cited, these all appear to be achalasia. Zenker and von Ziemssen classified them in two different categories, according to the presumed etiological factors. At that time four authors had published descriptions of simple "stenosis"—von Blasius, Cruveilhier, Hilton Fagge, and Wilks. (The case of the latter figures in both chapters!) The findings in the four cases of simple stenoses were similar according to Zenker and von Ziemssen, inasmuch as there was a narrowing at the cardia, with a proximal distention of the esophagus. This was thought to be a congenital lesion. The authors also note that in Cruveilhier's case, no change of the tissues at the point of narrowing was noted grossly. In this case the proximal distended esophagus showed polypoid vegetations of the mucosa. In Fagge's case, a squamous cell carcinoma of the distended proximal esophagus was demonstrated. This patient had suffered with dysphagia for 40 years. The "simple dilatations of the oesophagus" were thought to be due to a diminished contractility of the esophageal musculature, and the cause for this to be a "chronic catarrh" involving the muscularis. On the other hand, both Zenker and von Ziemssen also thought that the "chronic catarrh" might be a consequence of something else, not known as yet.

In 1882, von Mikulicz[163] presented the use of the gastroscope and esophagoscope "with demonstrations on the living," before the Eleventh Congress of the Deutsche Gesellschaft für Chirurgie. He also described the picture found in achalasia of the esophagus by endoscopic examination, and christened the condition "cardiospasm." An interesting sidelight of this presentation was von Mikulicz's claim to priority of discovery of the gastroscope, which he had planned according to the instruments devised by Nitze and Leiter for the

bladder. Von Mikulicz's claims of priority were challenged by Baratoux of Paris, who stated that Trouvet had used a gastroscope many years before. This von Mikulicz refuted by saying that the Trouvet instrument was not a true gastroscope, but only part of an instrument called "polyscope." Moreover, the tube was rigid, and hence useless in gastric work, and its use as a gastroscope had not been described.

Following von Mikulicz, Rosenheim[136] in 1899 also described the use of the esophagoscope in the diagnosis of cardiospasm. Roentgen's discovery was announced in 1895 and by 1897, Rümpel[138] had used a contrast swallow with "300 c.c. of 5 per cent bismuth subnitrate" to demonstrate the disease by the x-ray.

From then on publications on the subject became more and more frequent, and, in 1900, Neumann[110] gave a comprehensive discussion of the disease, having collected 70 cases, mostly in the German literature. In 1914 Geppert[42] was able to add 70 more cases, and in 1921 Thieding[155] collected a total of 315 cases in the world literature. He estimated that this number could easily have been doubled, had all the cases been published.

ETIOLOGICAL CONCEPTS

The etiological explanations in the early cases were vague and unsatisfactory. Today, although one theory has gained fairly general acceptance (failure of relaxation), there remains much that is unexplained or only putative.

Purton,[122] Hannay,[50] and von Rokitansky[165] noted that the immediate cause in their cases seemed to have been contusion of the chest. Others have noted the relationship of external trauma to the disease, or at least, to its onset. Lehmann,[84] in 1931, listed such factors as trauma to the chest, lifting of heavy objects, psychic trauma, and poor digestive habits. He thought that such factors make manifest a disease which might be congenital in character, and dormant up to the time of appearance of the first symptoms. Von Haberer[161] observed a case in a 40-year-old man who had been in an airplane crash in the first World War, and had suffered only a fracture of the mandible. Six to seven weeks later, the first symptoms of achalasia appeared. Von Haberer performed a thoracic esophagogastric anastomosis, and found the stricture one hand's breadth above the diaphragm.

Others thought that the primary cause might be congenital. Proof of this was sought in the fact that some cases occurred in infants or even newborn babies, that some patients had suffered since childhood, and, finally, that associated dilatations were found in other organs. Held[55] thought that the vegetative system is "below par by inheritance" and also that an "inborn status asthenicus or thymico-lymphaticus" is often responsible. Langmead[81] had a case in which the symptoms occurred directly after birth, and the diagnosis was confirmed at 16 months by x-rays and esophagoscopy by Mr. Addison. Langmead[82] recorded another case in a 13-year-old girl who had had trouble since birth. King, in 1955[75] reported a successful Heller operation in a 9-month-old infant. Weber[169] reported a case in a 5-year-old boy. In 1911, Morgan,[105] had collected the 5 cases known in infants under the age of 2 years. Some of the cases cited in this group might be considered questionable by our

present-day criteria. Morgan's own case was that of a baby who had had persistant vomiting since the third week after birth. The baby was in poor condition, and the author restored her by tube feeding. After satisfactory improvement was obtained, the author used larger and larger tubes so "as to create a stretching effect of the cardia." The child recovered under this therapy. Zenker and von Ziemssen[181] attributed their cases of "Stenosis Oesophagi" to a congenital factor, without stating the precise character. Hansen[51] reported in 1933 the history of a 7-year-old girl with typical history and radiologic findings. Medical therapy had failed and an esophagogastric anastomosis was performed with entire success. In his publication the author also mentions a 10-year-old child described by Rovsing. Frey[35] observed cardiospasm and severe bronchiectasis in a 19-year-old girl weighing 36 kilograms when she was admitted to the hospital. At autopsy there was found a microscopic cartilage deposit around the cardia, and this was regarded as congenital in character. Brunner[16] thought that 3 cases of associated megacolon and megaureter observed by Etzel in 16 autopsies of patients with megaesophagus spoke in favor of a primary congenital cause. In 1925, Hamilton Bailey, at the instance of Walton,[166] reviewed all the postmortem records of the London Hospital and found 6 cases of congenital pyloric stenosis in whom there was also marked dilatation and hypertrophy of the lower esophagus. Sweet[154] and Benjamins[10] observed cases of achalasia associated with pylorospasm.

Von Mikulicz[163] was responsible for the term "cardiospasm," and thought that a true spastic contracture prevented the food from entering the stomach. At the time (1882), he had observed some 6 or 7 cases personally, and mentioned 18 total cases published in the literature. The theory of spasm found rather wide acceptance in Germany, England, and the United States, and may have been the cause for a certain orientation in the surgical treatment of the disease. At present the theory of primary spasm is one of the least accepted ones, although Wangensteen[167] considers that the difference between spasm and failure of relaxation is a rather academic question. Spasm was incriminated by others who thought that it might be secondary to local inflammation, as spasm of the anus is secondary to a fissure, and pylorospasm may be secondary to a duodenal ulcer (Martin[95]). Von Luschka[162] ascribed one case to severe "catarrh" of the esophagus. At necropsy multiple erosions were found, and the esophagus was dilated as well as thickened. Rosenheim[136] described a case in which the "spasm" was thought to be due to a cold in a 55-year-old man. The patient had dark urine associated with trouble in swallowing. This occurred several winters in succession and the patient was found to have hemoglobinuria. He was relieved of his symptoms by entering a warm room. Zenker and von Ziemssen[181] thought that the cases of "simple dilatation" were due to a primary atony, and that the "spastic closure" was secondary to the esophagitis produced by the ectasia. Others again spoke of reflex spasm[144] by irritation from other diseased organs, such as gastroduodenal ulcers,[13, 46] gall bladder disease,[13] fissures[32, 46] near the cardia, hernias, and ptosis of the intestine.[32] Zaaijer[180] notes in his cases the frequent combination with gastric ptosis, and thinks that this factor in itself is enough to disturb the cardial opening reflex.

Many authors sought a purely anatomic cause in the production of achalasia. Handford[49] described a case in 1888 of a 52-year-old man; the specimen is now preserved at the Museum of the Royal College of Surgeons. The heart was much enlarged and dilated. The esophagus was dilated, except at its passage through the diaphragm. The aorta was also dilated and atheromatous, and Handford thought at the time that the aorta, by pressing the esophagus against the central tendon of the diaphragm, produced the dilatation. Mosher,[107] writing in the *Pennsylvania Medical Journal* in 1923 on the basis of careful anatomic studies, thought that the disease was due to stricture of the esophagus in the "liver tunnel." Jackson[70] thought that the diaphragm was at fault, and that the trouble lay either in overactivity, failure of relaxation, or incoordination of the diaphragmatic crura. Austoni[8] also incriminated the diaphragm.

At present, however, most authors agree that in almost every instance achalasia of the esophagus has a neural pathogenesis, resulting in an absence of relaxation of the cardial sphincter. Based on the work of Kronecker and Meltzer[77] on the physiology of swallowing, Einhorn[25] came to the conclusion in 1888 that we are dealing with "a lack of reflex relaxation during the act of swallowing." Little notice of this was taken until 1896, when Rolleston,[134, 135] independently of Einhorn, came to the same conclusion. He called it "a failure of coordinating mechanism, by which the cardia sphincter is normally relaxed during the act of swallowing." Following him, and oblivious of his two predecessors (as he states in a later publication), for the third time the suggestion was made in 1913, by Hurst[69] that the condition was one of nonrelaxation of the cardia. In 1915, at Sir Cooper Perry's suggestion, Hurst introduced the term of "achalasia"–absence of relaxation. Due to his observations and pathologic studies,[63, 67-69] and the experimental work of Rieder[126-132] whose studies complemented Hurst's, the "absence of relaxation" is generally accepted today[2, 6, 11, 16, 35, 46, 48, 56, 59, 152, 161, 180] as the mechanism of production of esophageal dilatation in achalasia.

Rieder,[131] in his only case of vagotomy for achalasia in 1929, had noticed, like others, that matters became worse instead of better. The failure of the cardia to relax became even more accentuated. Experimentally he sectioned all of the vagus and its branches to the cardia and precardia, and obtained in the animals thus treated, the clinical picture of marked delayed emptying. However, in all cases, a certain autonomy returned, because of the independence of the lower (intramural) esophageal plexuses. Histologic examination[130] of the intramural plexuses after experimental vagotomy showed degeneration of the corresponding ganglia. Adjacent to the altered ganglia were found intact autonomous ones. Rieder found the same degeneration in clinical cases of achalasia. He used the Bielschowsky-Gross stain, and took the material as soon as possible after death because of its rapid postmortem changes. In 2 proved human cases he found histologic changes in the nuclei and cytoplasm of the ganglion cells. The nerve fibers showed degeneration similar to that produced by vagus section.

Hurst,[69] in 1924, had recognized this influence of the vagus and suggested "that the majority of cases are caused by progressive organic disease involving Auerbach's plexus." In 1926, Rake,[123, 124] working in the laboratory of Adrian Stokes, observed lesions of subacute inflammatory nature, and larger ganglia than usual on microscopic examination. There was also noted an increase in cellularity of the nerve sheaths. In the following years, 10 more specimens were examined by them and all of them showed inflammation, degeneration, and even fibrosis of the plexuses.

On the basis of all this, Rieder[131] came to the following conclusions: (1) The physiologic function of the cardia is to close the esophagus from the stomach to prevent reflux. (2) The cardia, when at rest, is closed, and opens only in a reflex fashion under the influence of deglutition. (3) Vagotomy in animals produces the clinical picture of delayed esophageal emptying, because of interference with the opening reflex, as proved by barium swallow. (4) The same picture is obtained if the vagal rami to higher levels of the esophagus are interrupted, because the opening reflex is only part of the peristalsis of the esophagus during the act of swallowing. (5) Function of the cardia after experimental vagotomy may re-establish itself because the lower esophageal ganglia become partly autonomous. (6) Cardiospasm is not a spasm, but only a physiologic closure between meals. The disorder lies in the fact that the opening (relaxation) at the time of deglutition does not occur. A continuous "spasm" at the cardia is nonexistent. The cardia has functions like the sphincter ani and the vesical sphincter.

As to the reasons why this inflammation and degeneration of the nerve cells of the plexus occurs, many theories have been advanced. It has been suggested that the inflammation spreads to the plexuses from the esophageal lumen. However, in early cases no esophagitis is present and nerve cell degeneration is present.[69] Syphilis, as in so many other conditions, was incriminated by some. Of interest is the observation of Etzel[26] in Brazil. He found a frequent association of megaesophagus with megacolon, and/or megaureters which he attributed to a vitamin B deficiency. In pigeons fed a vitamin B-deficient diet, he found the same microscopic alterations of the esophageal Auerbach plexuses that Rieder and Hurst found. He himself saw one case of achalasia, associated with pylorospasm and megaureters.

Vampré[159] also in Brazil, states that the disease is so frequent in the interior of Brazil that it seems endemic. This author has noticed that the disease is found in those Brazilians who live on a diet rich in flour and salted dried meat. Vampré points out that, while constant trauma to the esophagus might initiate the disease, it is more probably due to a parasitic infection, since the disease is endemic in the wilder parts of Brazil, and the patients show an associated splenic hypertrophy and a secondary polyneuritis.

Of interest also are the experimental findings of Deloyers and associates,[24] who were able to produce cardiospasm in cats similar to the disease in human beings and with the characteristic microscopic lesions by injecting 2 ml. of 5 per cent phenol into the esophageal well.

Alnor[5] was able to produce similar results in dogs by applying carbon dioxide snow locally to the region of the cardia (–80° C. for ½ minute). At postmortem examination there was no cicatrix.

The rather confused situation in the definition of the etiology of achalasia may be best indicated by the many terms given the disease: cardiospasm, achalasia, megaesophagus, angina convulsiva, oesophagospasmus, phrénospasme, rétrécissement spasmodique, stenosis spastica fixa et migrans, idiopathic dilatation, dystonia, dolichoesophagus, congenital dilatation, primary atony, dysphagia paradoxa, and so forth.

Even today a certain nomenclature persists and indicates so well the early theories, called "Kardiospasmus" in Germany, it becomes "megaoesophage" or "dilatation idiopathique" in France, and is referred to as "achalasia" in England, and as "cardiospasm" or "achalasia" in this country.

TREATMENT

(Outline of Ochsner and De Bakey[112] amplified, verified, and brought up to date.)

I. Nonoperative
   A. Medical: Of historic interest only
   B. Dilatation:
      1. Thomas Willis,[175] 1679: whale bone bougie
      2. Sir Astley Paston Cooper,[122, 174] 1821, 1866: bougies
      3. Plummer,[119, 120] 1908, 1912, and Moersch,[104] 1936: hydrostatic dilator
      4. Starck, 1934: "Starck dilator"
      5. Henning,[61] 1934: "flexible dilator"

II. Operative:
   A. Operations directed at the dilated esophagus:
      1. Excision of the wall:
         a. Jaffé,[71] 1897, proposed full-thickness longitudinal excision of a strip (Fig. 1).
         b. Reisinger,[125] 1907, resected a full-thickness, 15 by 2 to 3 cm. longitudinal strip, in two stages (Fig. 1).
      2. Esophagoplication and invagination:
         a. Freeman,[31] 1923, performed a vertical plication by invaginating an upper segment of esophagus into the thoracic esophagus through a cervical approach (Fig. 3).
         b. Reisinger,[125] 1907, intended to do a longitudinal plication, but performed a longitudinal excision (see above).
         c. Willy Meyer,[100, 101] 1911, 1912, in 3 cases performed a longitudinal plication through a thoracotomy under differential pressure at the German Hospital (now Lenox Hill Hospital) in New York (Fig. 1).
      3. Esophagostomia thoracalis: Zaaijer,[179] 1912, in a 2-stage operation, for drainage of a large esophagus, initially thought to be a diverticulum, created a posterior thoracic esophagostomy (Fig. 1).

B. Operations directed at the nerve supply:
   1. Vagolysis: Willy Meyer,[101] 1911, thought that "forcible separation of the vagus from the esophageal wall" is of importance (Fig. 1).
   2. Vagotomy:
      a. Rieder,[131] 1929, performed this procedure once, through a thoracic approach (Fig. 1).
      b. Rudler,[137] 1950, in cases of failure of the cardiomyotomies or esophagogastrostomies, advised an added vagotomy.
   3. Sympathectomy: Knight,[76] 1935, and Adamson,[1] 1935 (Fig. 1).

C. Operations directed at the cardia:
   1. Dilatation:
      a. Retrograde and anterograde: Martin,[95] 1901, through a gastrostomy (Fig. 2).
      b. Transgastric:
         (1) Von Mikulicz,[164] 1904, through a gastrotomy (Fig. 2).
         (2) Schäfer,[143] 1920, digital dilatation of the cardia through the invaginated unopened stomach (Fig. 2).
      c. Extramucosal cardioplasty: (analagous to Fredet-Weber or extramucosal Heineke-Mikulicz pyloroplasty).
         (1) Gottstein,[45] 1901, proposed this operation, but he did not perform it (Fig. 4).
         (2) Girard,[44] 1915, performed the operation.
   2. Invagination:
      a. Tuffier,[157] 1922, pulled down the esophagus and invaginated it into the stomach and corrected the gastric ptosis by fixing the lesser curvature to the gastrohepatic ligament (Fig. 3).
      b. Kardiendyse: Lotheissen,[91] 1935, invaginated the "stenosed" cardia into the stomach, following an anterior incision of the cardia through all layers and suture of the lips of the incision (mucosa to serosa through muscularis) (Fig. 3).
   3. Plastic procedure:
      a. Cardiomyotomy: (rationale similar to the Ramstedt pyloromyotomy for hypertrophic pyloric stenosis).
         (1) Gottstein,[45] 1901, proposed, but did not perform the operation.
         (2) Heller,[57] 1914, did the first such procedure (anterior and posterior incision) without knowledge of Gottstein's work (Fig. 4).
         (3) De Bruine Groeneveldt,[15] 1918, was the first to practice an anterior incision only (Fig. 4).
         (4) Zaaijer,[177] 1923, popularized this idea. Modifications have been described by many authors. For these we refer to the section "History and Modifications of Heller's Procedure."
      b. Cardioplasty: (analagous to the Heineke-Mikulicz pyloroplasty).
         (1) Georg Marwedel,[96] 1903, attempted to do a cardioplasty, but the "spasm" was located above the diaphragm, and could not be reached from below (Fig. 4).

(2) Wendel,[173] 1910, did the first cardioplasty (Fig. 4).

(3) Sencert and Simon,[147] 1921, performed cardioplasty after pulling down the elongated esophagus and fixing it in its new position around the esophageal diaphragmatic hiatus.

4. Excision:

a. Rümpel,[138] 1897, proposed excision of the cardia and esophagogastrostomy (Fig. 5).

b. Pribram,[121] 1922, described excision and esophagogastrostomy done on Nov. 22, 1920, by Bier.

c. De Oliveira,[113] 1955, performed "esophago cardiac sphincterectomy" leaving the mucosa intact (Fig. 5).

5. Esophagogastrostomy:

a. Hans Heyrovsky,[65] 1913, performed lateral anastomosis (Fig. 6).

b. N. B. Gröndahl,[47] 1916, modified the operation, so that the anastomosis is performed in a fashion similar to the Finney gastroduodenostomy, in order to avoid spur formation (Fig. 6).

c. Lambert,[80] 1913, produced a cardiac spur crush with a clamp (Fig. 6).

d. Sauerbruch and Henschen,[142] 1932, used the thoracic approach.

D. Bypass procedure:

Kümmell,[78] 1921, carried out an esophagojejunostomy "antethoracic" with transposition of the stomach, and cervical gastrostomy. The procedure was a failure. He planned to perform a cervical esophagogastrostomy (Fig. 7).

E. Operation directed at the cardia, the acid-bearing stomach, and esophagitis: Wangensteen,[167] 1951, excised the lower esophagus, the acid-bearing stomach portion, and added pyloromyotomy (Fig. 5).

F. Operations directed at the postoperative esophagitis, following one of the preceding operations for achalasia:

1. Esophagojejunostomy: Barrett,[9] 1949 (Fig. 7).

2. Interposition of jejunal segment: Merendino,[98] 1955 (Fig. 7).

Through the years most authors have agreed, and still agree, that approximately 70 to 80 per cent of all cases are curable by one or several dilatations (Nissen[111]). Of interest are the early attempts of Willis (whale bone) and Sir Astley Paston Cooper, 1821, 1866, the use of bougies and sounds by Rosenheim,[136] Gottstein,[45] and many others. The only lasting results obtained by dilators, however, are those produced by an instrument capable of furnishing a sudden and rather violent effort, "producing a mechanical fracture of the cardia."[149] The most popular instruments are the Starck dilator[148, 149] on the Continent, and the Plummer hydrostatic sound,[119, 120] as used by Moersch[104] and Olsen,[114] here in the United States. Plummer reported 11 cases as early as 1906. Forceful dilatation, however, is not always without danger, and ruptures have been reported.[104, 114]

Most of the operative procedures, directed at overcoming the obstacle at the cardia, are based on purely mechanical factors, and were devised in Germany before the first World War.

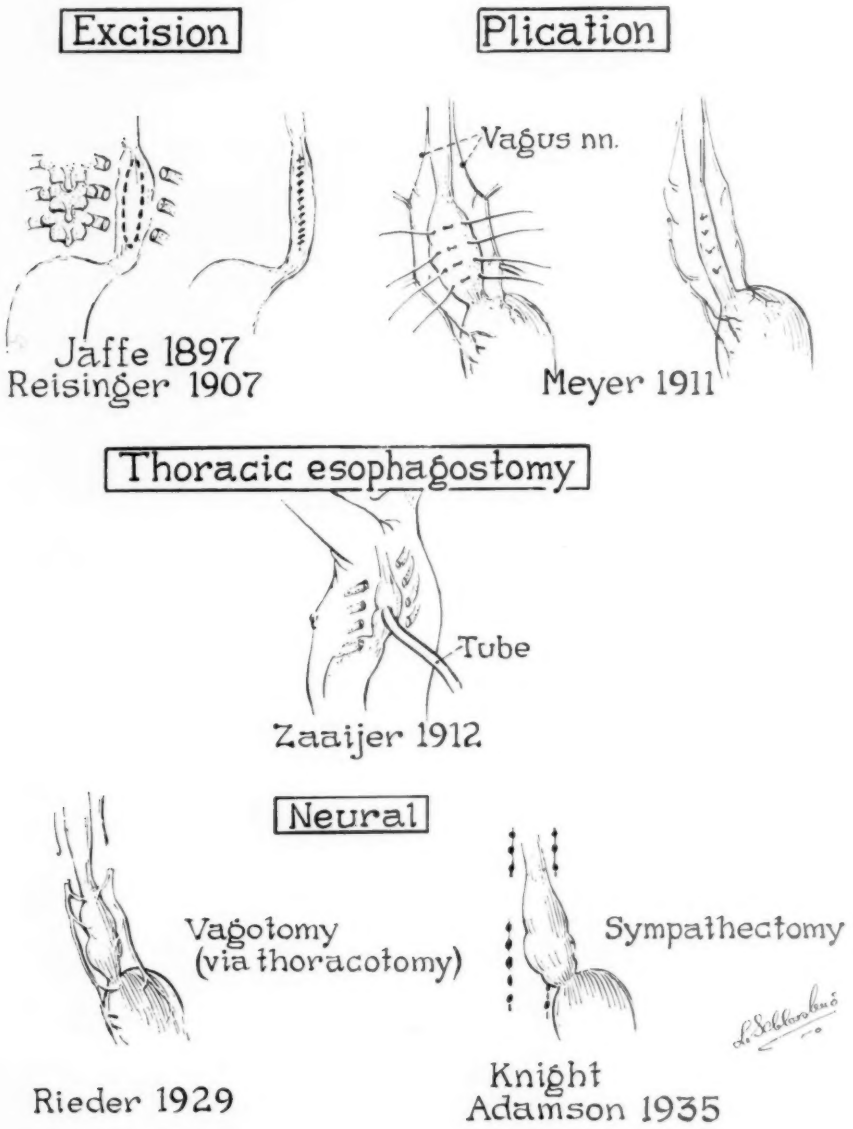

Fig. 1.—Jaffé suggested a full-thickness longitudinal excision of a band of esophagus. It was Reisinger who resected, in a two-stage extrapleural procedure, a 15 by 3 cm., full-thickness strip with improvement.

Willy Meyer, using the Sauerbruch Chamber at the German Hospital, New York, performed a transthoracic double longitudinal plication of the dilated esophagus, with concomitant separation of both vagus nerves from the esophagus. In 3 cases done that way, all the patients were able to swallow, although one of them had to take water before each meal, and one died a year later with mediastinitis, after fistula formation.

Zaaijer, thinking that he was draining a large esophageal diverticulum in a pregnant woman with a history of dysphagia of 9 years' duration, created a posterior thoracic esophagostomy, in two stages, after preliminary gastrostomy.

Rieder performed a transthoracic vagotomy, with aggravation in the patient's condition. This made him reject the operation and investigate the physiology of the cardia.

Knight and Adamson divided the splanchnic nerves in the chest, and claimed early good results.

Martin's[95] suggestion, in 1901, of gastrostomy, combined with ante and retrograde dilatations, and von Mikulicz's technique[164] of gastrotomy, with retrograde manual dilatation in 1903, soon gave rise to severe criticism. The advantage over simple dilatation was nil, at the price of a greater operative risk and morbidity. In one instance, Galpern,[39] 1930, from Dnepropetrowsk, Ukraine, observed esophageal bleeding immediately following a Mikulicz procedure. The bleeding was observed during the procedure as coming from the cardia after the manual dilatation had been done. The operation was hurriedly completed and the patient had two postoperative transfusions (one of 150 c.c. and the other of 400 c.c.).

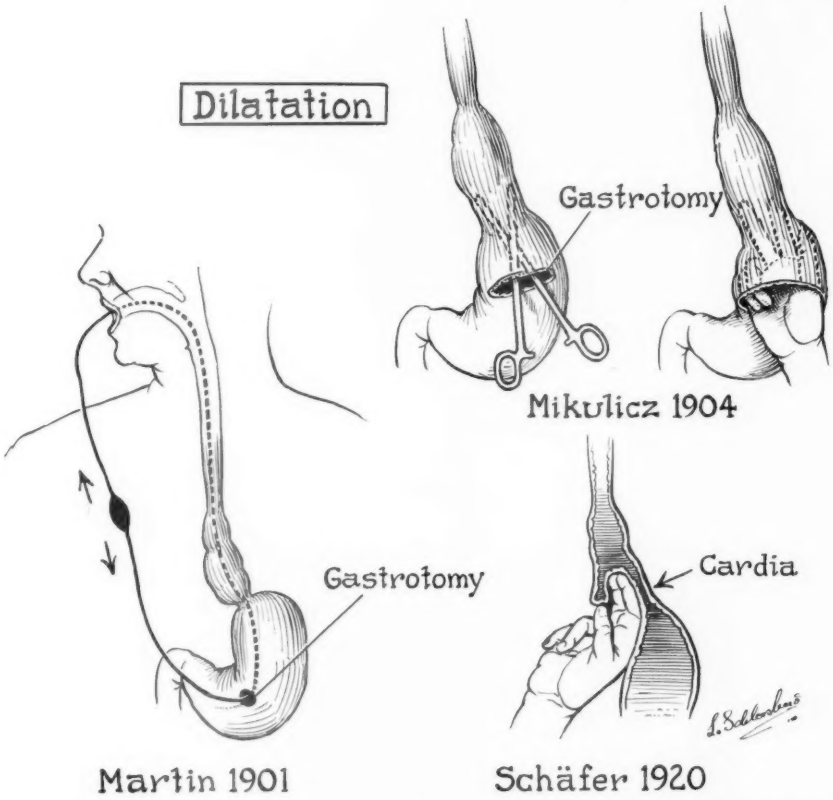

Fig. 2.—Martin performed a gastrostomy, followed by retrograde dilatation and irrigation, and then the introduction of an orogastric string. An attached olive permitted ante and retrograde dilatation. For Martin it appeared important to eliminate the esophagus temporarily by doing the gastrostomy.

Through a gastrotomy, von Mikulicz dilated the cardia with a forceps first, until it admitted two fingers. The gastrotomy was closed primarily. A girl thus treated in February, 1903, had good relief. However, others[39] rejected this technique because of operative hemorrhage and poor final results.

Schäfer modified this technique so as to avoid the necessity for opening the stomach by introducing two fingers into the cardia through the invaginated anterior gastric wall. This he followed by postoperative dilatation with esophageal sounds.

Schäfer[143] dilated the cardia at laparotomy through the invaginated stomach, without opening it.

In 1897, Rümpel[138] proposed approaching the cardia by lifting up the left costal margin and treating the disease by resection of the cardia. In the same

year, Jaffé[71] criticized Rümpel's idea. He considered longitudinal excision of a full-thickness strip, but did not do such a procedure, and actually voiced his preference for retrograde dilations with sounds.

In 1907, Reisinger[125] presented, before the German Association of Surgery, a patient who had had symptoms for 12 years. A Witzel gastrostomy had been done in 1905. On Nov. 20, 1905, the posterior mediastinum was opened to avoid a transpleural procedure. The author had planned to do a plication, but the

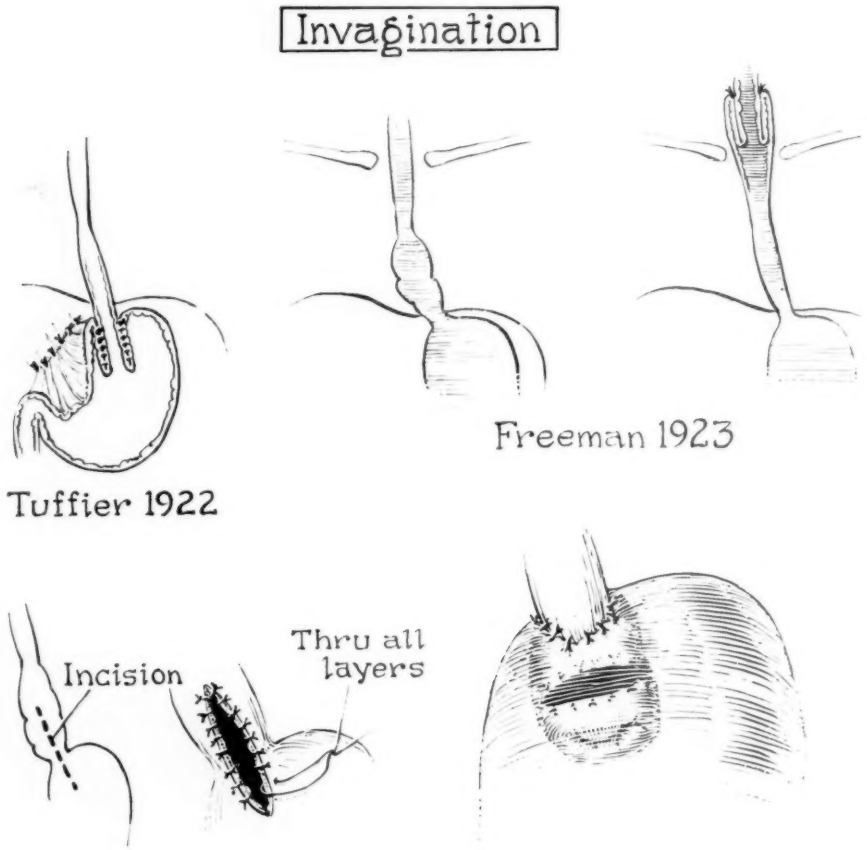

Fig. 3.—Tuffier pulled the elongated esophagus into the abdomen, invaginated it into the stomach, and maintained it in its new position by a circular row of sutures. In one case treated this way, the patient gained 12 Kg. of weight, but the author himself was very critical of this method, since postoperative roentgenograms still showed slowing of the barium in the lower esophagus.

Through a vertical left cervical incision, Freeman delivered the dilated and elongated thoracic esophagus into the neck, invaginated the cervical esophagus into the thoracic one, and kept the new position by a circular row of chromic catgut. Twenty years later the patient had only occasional dysphagia.

Lotheissen liberated the elongated esophagus into the abdomen in one case, then sutured the fundus of the stomach to the posterior aspect of the esophagus above the stricture. This was followed by a longitudinal section of all layers of the cardia anteriorly, and suture of the lips of the incision (mucosa to serosa through muscularis). Finally, the invagination was completed anteriorly, the fundus was sutured to the esophagus above the cardioplasty, and the incision left open. Good healing was observed, and the patient took milk on the fourth postoperative day. Of some 120 patients observed, however, this author operated only twice: the second operation was a single "Kardiolyse" for questionable achalasia.

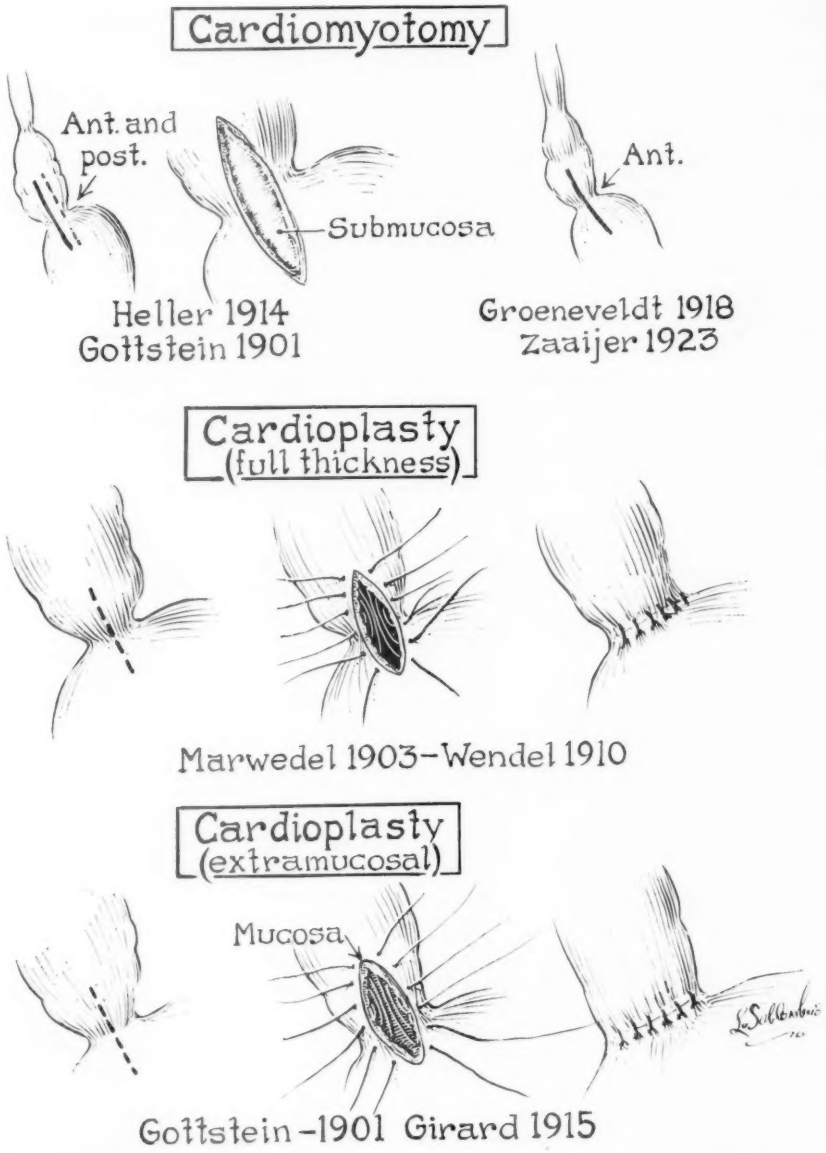

Fig. 4.—Heller performed his first cardiomyotomy, analogous to the Ramstedt pyloromyotomy with an anterior and a posterior incision, on April 14, 1913. The operation had been previously suggested by Gottstein. The incisions were 8 cm. long, and did not include the unchanged submucosa. On the day following operation the patient ate bread, meat, and potatoes. Three months later he had gained weight, but the lower esophagus continued to be S shaped. In 1921 this first patient was still well. He had to eat slowly and a barium swallow showed some narrowing at the cardia.

De Bruine Groeneveldt modified Heller's technique to an anterior incision only, with good results, and Zaaijer popularized this method. He reported on 8 cases operated on in Holland with good results and no mortality, in the *Annals of Surgery*.

Marwedel attempted, and Wendel first performed, a longitudinal section through all the layers of the cardia, with transverse closure (analogous to the Heineke-Mikulicz pyloroplasty). This patient took fluids on the fourth postoperative day, and the gastrostomy tube was removed on the fifteenth postoperative day. The patient gained 50 pounds subsequently, and had no complaints.

Gottstein proposed, and Girard performed a longitudinal section of all the layers of the cardia, down to the mucosa, with transverse suture leaving the mucosa intact (analogous to the Fredet-Weber, or extramucosal Heineke-Mikulicz pyloroplasty).

Girard operated twice, using this technique in 1914 and 1915, respectively. In the later case he perforated the mucosa and this was covered with a piece of omentum, sutured in place.

patient "collapsed" and the operation was abandoned, after several silk slings had been left around the esophagus for better recognition at a second operation. A second procedure was undertaken in January, 1906. He resected a longitudinal strip of esophagus, 15 by 2 to 3 cm. The patient was much improved once he recovered from this second procedure, an incredibly bold one for the time. Later on such operations as pulling down of the esophagus, with invagination into the stomach, and fixation to the wall of the stomach (Tuffier[157]), or with cardioplasty (Sencert[147]), vagotomy, and sympathectomy were advised. But all of these have lost their authority, or even their "raison d'être," although some of them persist as complementary steps in more complex procedures.

In 1903 Marwedel[96] described a new approach to the upper abdomen by lifting up the costal margin as a hinged flap. In a 20-year-old patient with cardiospasm for whom cardioplasty had been planned, he found the site of the disease to be so high above the diaphragm that it could not be reached from

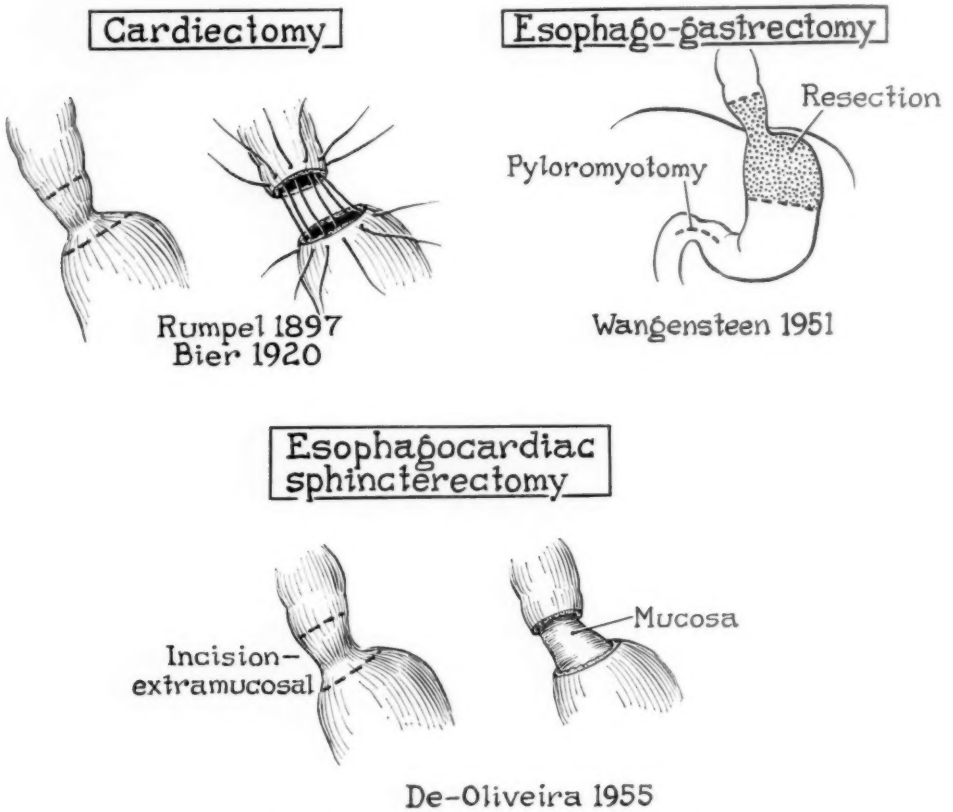

Fig. 5.—Rumpel suggested excision of the cardia. This operation was performed by Bier, as reported by Pribram. The patient died of cardiac failure the day following the operation.

Wangensteen proposed the most radical procedure in the treatment of achalasia, excision of the lower esophagus and the acid-bearing portion of the stomach associated with a drainage procedure. He obtained good results in the first 7 patients, but he has since returned to using the Heller procedure.

De Oliveira performed an esophagocardiac sphincterectomy. This operation can be considered as an extended Heller procedure, and consists of a circular excision of all layers, at the site of the narrowed cardia, leaving the mucosa intact. Of 130 patients, he reported 71 cures, 33 improvements, and 7 failures. Fifteen patients were lost to follow-up and 4 died.

below. In 1910, Wendel,[173] apparently independently of Marwedel's suggestion, performed a successful cardioplasty on a 46-year-old patient with concomitant gastrostomy.

Heyrovsky,[65] in 1913, was the first to describe esophagogastric anastomosis in the treatment of achalasia. He performed the first operation on a 34-year-old female on June 22, 1909, this was followed by a second case on Nov. 24, 1910, and a third case on Oct. 14, 1912.

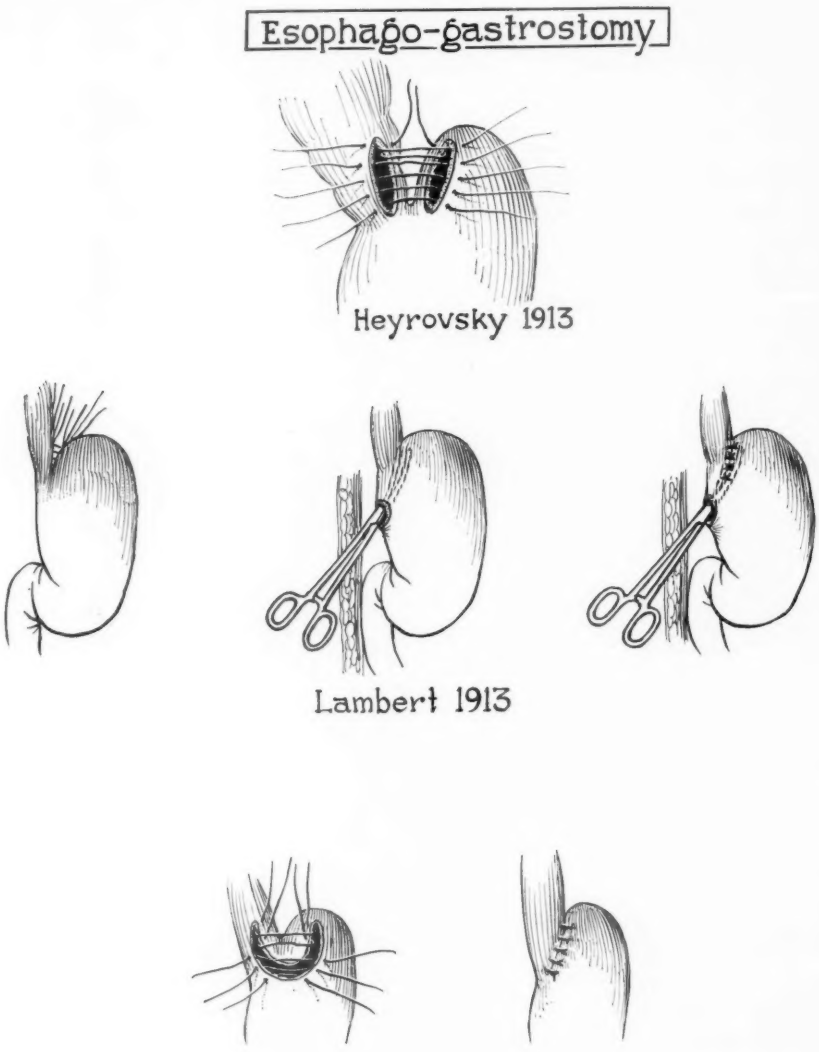

Fig. 6.—Heyrovsky first described the side-to-side esophagogastrostomy. This procedure has long been, for many, the operation of choice. He had performed 3 such procedures prior to his publication, all with good results. Since then, the procedure has undergone many modifications.

Sauerbruch and others performed the operation through a thoracic approach. Many attempted to avoid the creation of a spur; Lambert did so by crushing it with a clamp, left in the stomach, and brought out through a gastrostomy and the abdominal wall. This clamp was removed on the eighth postoperative day.

Gröndahl obtained the same result by fashioning a anastomosis similar to the Finney pyloroplasty.

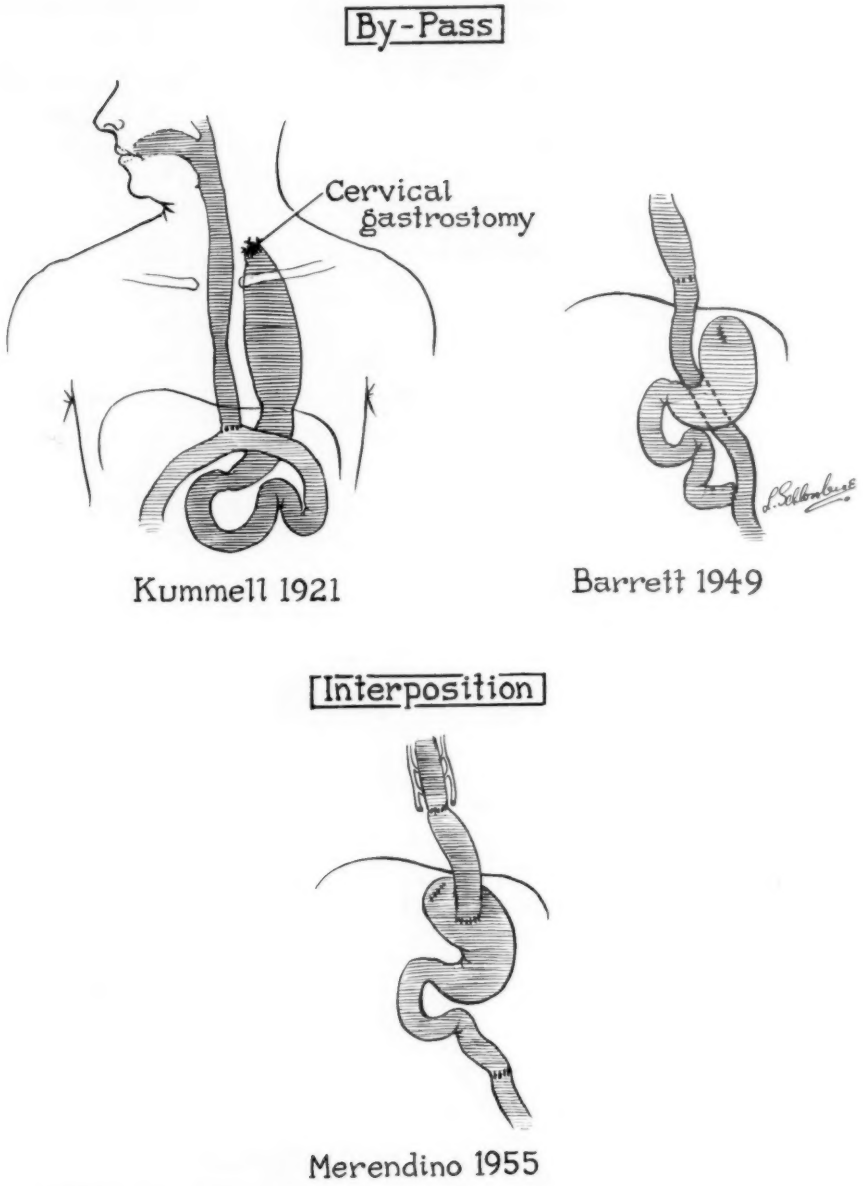

Fig. 7.—Bypass procedures have been devised by some to relieve the patients of the complications of ill-conceived initial operations, other than Heller's. In one patient who had shown no improvement after several dilatations and one Mikulicz manual dilatation, Kümmell performed an esophagojejunostomy, and transposed the stomach into the neck, where it was brought out as a cervical gastrostomy. The patient was able to take food by mouth and gastrostomy. However, 2 months after the initial operation, he was unable to swallow food and the author then decided to anastomose the stomach to the cervical esophagus.

Barrett had to perform an esophagojejunostomy, excluding the stomach from the food circuit, in a patient who needed successively over 100 units of blood, after 5 unsuccessful previous operations, which had created and then aggravated severe esophagitis. Allison has used this procedure extensively.

Merendino's excision of the esophagogastric junction with interposition of an isoperistaltic segment of jejunum, bilateral vagotomy, and associated drainage procedure, is another example of a technique which has been successfully used by him, and others, in the treatment of complications, following the operative treatment of achalasia.

Gröndahl[47] in 1916 suggested a U-shaped incision, similar to the Finney pyloroplasty, in order to avoid formation of a spur.

Of interest are the techniques of Lambert[80] and Keller[73] in this country, the first one using a crushing clamp, the second a heavy fish line in order to cut through the spur.

Sauerbruch[142] used the thoracic approach for esophagogastrostomy.

Heller,[57] of Leipzig, published the first successfully performed "Extramuköse Kardioplastik beim chronischen Kardiospasmus" (1914). He remarked at that time that such an operation had been suggested by Gottstein[45] in 1901.

HELLER'S ORIGINAL PUBLICATION

Heller's first operative case was that of a 49-year-old patient who had suffered dysphagia for approximately 30 years. The patient subsisted mainly on a liquid diet, had repeated postprandial vomiting, and during one such episode aspirated, and suffered tracheal obstruction which was relieved by his physician.

On examination, a sound introduced into the esophagus encountered an obstacle at 42 to 44 cm. from the incisor teeth, but could then be passed into the stomach. A barium swallow showed stasis at the cardia.

On April 14, 1913, operation was undertaken. A Marwedel-type approach was used. After ligation of some of the branches of the short gastric vessels and of the left gastric artery along the lesser curvature, the cardia was pulled down into the abdomen. By blunt dissection a length of esophagus of about 10 cm. was mobilized and pulled down. Heller saw a "spastic contraction" extending over a segment of 3 cm. proximal to the cardia. Proximal to this the esophagus was dilated.

In spite of good exposure and sufficient mobilization of the esophagus, he decided against an anastomosis for several reasons. The wall of the esophagus in the region of the "hypertrophic, degenerated" musculature seemed friable and was not covered by any serosa. Also by analogy, the picture presented at operation evoked that of pyloric stenosis in children, and its treatment by extramucosal pyloroplasty (Ramstedt's paper had appeared the year before). Hence a longitudinal incision of the musculature of the anterior wall of the esophagus and fundus, down to the submucosa, was made (8 cm. in length) and a similar incision on the posterior aspect. The incisions were anterior and posterior, rather than lateral, in order to preserve the blood supply. The postoperative course was complicated by a bilateral, hypostatic pneumonia. The day following operation the patient took food, including solids. Three months after operation the patient was doing well and had gained weight. A barium swallow still showed slowing of the opaque medium at the cardia, and an S-shaped elongation of the lower esophagus.

The indications for this first case had been: (1) good general condition, (2) patient able to take liquid diet only, (3) social reasons, and (4) patient's demand for help.

Heller made the following observations on the requirements of a successful technique: (1) good exposure, (2) complete section of the muscularis without

traumatizing the vessel-carrying submucosa, (3) transverse suture was not necessary, and most often impossible, (4) sufficiently long incision, and (5) two incisions, anterior and posterior. By analogy a single incision of the sphincter ani does not disturb its function, but a double section does.

The advantages over other then-existent procedures were: no suturing in a difficult region, as in Wendel's cardioplasty technique, and freedom from contamination compared to von Mikulicz's transgastric divulsion.

As to the choice between the Heller and the Heyrovsky procedure, Heller thought at the time that the anatomic status found at operation should decide the operative tactic.

HISTORY AND MODIFICATIONS OF HELLER'S PROCEDURE

Following Heller's original publication, little enthusiasm for it appeared in the literature. It would be difficult, however, to evaluate the precise meaning of this, since, at that time, major surgery in general, and that of the esophagus in particular, was only being developed. In addition, the diagnosis of achalasia of the esophagus was probably established less frequently than today. The anastomotic procedures, mainly the Heyrovsky technique and its modifications, gained general recognition and acceptance during the twenties and thirties.

The infrequency of surgical attack is attested to by the collective review of Payr[117] in 1929. He was able to collect only 169 operations in the literature up to that time. There were 29 esophagogastrostomies, with 22 reported good results; 59 cardiomyotomies, with 42 good results; 60 Mikulicz procedures, with 48 good results; 18 cardioplasties, with 12 good results; and 3 esophagogastric anastomoses, with crushing of the spur. In the same year, Fromme[36] observed that one of the reasons why more cases were not treated operatively was that the patients were so largely seen by the otorhinolaryngologists, an opinion which Santy[139] confirmed only very recently. In 1924 Starck had treated 100 cases and 252 cases in 1931,[150] and Plummer (1921) 301 cases, by the dilatation techniques described by them. By 1934 Starck[148] had reported 338 personal cases, and at the Mayo Clinic, up to January, 1936, 948 cases had been treated by dilatation (Moersch[104]). In 1951 Olsen[114] and associates reported another 601 consecutive cases treated by dilatation from Jan. 1, 1935, to Jan. 1, 1947.

In Germany Heller was a prophet without honor. Although reports of use of his technique never disappeared entirely, it would seem that the anastomotic procedures were given a greater impetus under the influence of Sauerbruch (thoracic approach) and his pupil, Frey (crushing of the spur). Following his first report, Heller published additional papers. In 1921[58] his first patient had been re-examined, and had been found in good state of nutrition, asymptomatic and capable of eating any kind of food, provided he ate fairly slowly. Radiologic examination showed some narrowing at the cardia. At the time, 16 Heller procedures had been reported by the author and other surgeons, in and outside of Germany. Failures were reported in four cases; one was due to stenosis secondary to a scar at the esophageal hiatus, and the three other failures were

in early cases with only "slight dilatation and spastic contraction." Therefore, Heller advised that the operation not be carried out in early cases (without marked dilatation and anatomic changes in the lower esophagus). Heller took occasion to criticize Sauerbruch's vagotomy, because it resulted in a passive mid-position of the cardia, which also represented a hindrance to the act of swallowing. Other types of operations involved, according to Heller, all the then-current dangers of esophageal suture.

In 1932 Heller[56] indicated a clinical distinction between acute and chronic cases. Acute cases are often amenable to psychotherapy. In 1952 Heller[59] concluded that all patients should first have a Starck dilatation, with operation only if this failed. He also noted that recurrences had occurred after cardiomyotomy. Many authors, unnecessarily perturbed by the persistence of postoperative radiologic esophageal dilatation, admitted failure, and resorted to anastomotic procedures. Heller advised ignoring the roentgenogram, so long as the esophagus emptied well. Real stenosis, after operation, was due to a scar and not a tonic contracture, and should be treated by bougienage. Another reason, he thought, for lack of success, was failure to make a posterior incision, as well as an anterior one.

Other German authors reported early successful Heller procedures. Lindström[86] had one case in 1919, and Fromme[36] had two anterior cardiomyotomies in 1929. One of these had a partial recurrence, however, and that was one of the reasons why this author preferred anastomotic procedures. In the same publication he spoke about two closed and two open cardioplasties, and six Heyrovsky procedures, all of which were done apparently with good results. Fromme[38] reasserted his opinion again in 1933, by which time he had done 8 esophagogastric anastomoses by the abdominal approach. In a discussion on Fromme, Harttung[52] suggested that one of the major factors in achalasia was the presence of adhesions about the cardia. One case he treated, with lysis of the adhesions and cardiomyotomy, with good results. A second patient had had a Heller procedure, and 7 years later he complained again. Here also adhesions were found, and a Wendel cardioplasty was done with good results. In 1922, Finsterer[28] had warned against the danger of the "scarring stenosis" and adhesions. He had two such instances with recurrence in a Heller procedure, and concluded therefore that the Heller procedure was designed only for cases with "real spasm." During the same year, H. Meyer[99] gave his theoretical support to the Heller, Heyrovsky, and cardiac resection procedures. He thought that the latter was the soundest on the basis of etiology, but that both it and the Heyrovsky were difficult and had a high mortality.

In 1935 Fromme[37] still preferred the Heyrovsky technique because the dysphagia disappeared and the esophagus became smaller. Next best results were obtained with the Heller procedure. Fromme had treated a case operated upon by Heller himself in 1918. Fifteen years later, the patient had a large esophagus which emptied well, without dysphagia, but a sensation of pressure persisted. Sauerbruch attempted a transthoracic procedure in this patient, but death occurred on the table. Fromme, at that time, thought that if secondary

procedures were necessary they ought to be done through the chest. Most,[108] in 1928, reported one case of a Heller procedure in which the patient was found postoperatively to have an esophageal diverticulum, a megaesophagus, and a stenotic cardia. A Mikulicz procedure and removal of diverticulum took care of the problem. The author concluded that the Heller procedure was not always safe. In 1926 Crone-Münzebrock[23] stated that the Heller procedure gave good results. He intended to use it in 2 cases but he eventually did a Mikulicz procedure because of the "simplicity and lack of danger" attached to it.

Rieder,[127, 132] after one unsuccessful vagotomy, accepted Heller's technique as the method of choice. Rohde[133] reported a successful Heller procedure in 1934. Only in more recent years have the advantages of the Heller procedure been re-asserted in the German literature by the extensive analyses of Berchtold,[11] Brunner,[16, 17] and Alnor and Wanke.[6]

The interval was occupied in Germany largely by the different types of esophagogastric anastomoses, which, for Frey of Munich, constitute today the method of choice.[32-35] However, Frey[34, 35] concedes that the Heller procedure has its good points because of the generally good results and low mortality. Contraindications to it[35] would be organic stenoses, spasms at higher level, and, according to Sauerbruch, the congenital dilatations. Frey[34] does not see the rationale of a Heller procedure, since a hypertrophy of the muscularis is not found in achalasia. Frey would use the Heller procedure only in cases of gastric hyperacidity, and in all other cases an anastomosis with crushing of the spur, always attempting bougienage first. Frey observed only 3 cases of peptic ulceration of the esophagus in esophagogastrostomies.

The first warning of regurgitation in esophagogastric anastomoses was given by Finsterer in a discussion on Palugyay[115] in 1923, but the relationship of such regurgitation to esophagitis and ulceration at that time must not have been sufficiently appreciated for surgeons to take warning. In 1931 von Haberer[161] reported a thoracic esophagogastric anastomosis and said that failures of that technique through secondary stricture and reflux had been observed in other patients, although his patient did well. In 1936 Henschen[62] reported one case of thoracic esophagogastrostomy done in 1922, and the patient remained well until 1936, at which time she had melena and hematemesis. Laparotomy did not reveal a gastric ulcer and the author thought that the patient had an ulceration of the anastomosis, or peptic esophagitis, however, no other conclusions were reached.

In Russia and the Baltic countries, cardiomyotomy and anastomoses were both done. Mintz[103] in Riga reported 3 Heller procedures with good results in 1920, and, in 1929, Hesse,[64] one of Russia's most prominent surgeons, stated that the Heller technique was the most popular in Russia, although he would not himself use it because of fear of trauma to the mucosa, secondary rupture, and "Durch wanderungs peritonitis." Around 1930, Ambrunjanz[7] suggested performance of a Heller myotomy over a finger introduced into the stomach. More recently, Khodkov[74] returned to the original Mikulicz procedure.

The same pattern holds true for the Scandinavian countries, where Schaldemose[144] of Copenhagen performed one Heller procedure in 1916 with good

result. Bull,[18, 19] reported 3 esophagogastrostomies in 1925. In a fourth case the original plan had been to do a Heller procedure, but the mucosa was perforated and a cardioplasty was done. Complete obstruction ensued, which was relieved one year later by an esophagogastrostomy. Hansen[51] reported an esophagogastrostomy in a 7-year-old girl in 1933, with good result. In 1952 Gertz and Tyge[43] of Stockholm re-evaluated 22 patients and stated that since February, 1949, they had returned to the Heller procedure, for the same reasons which led Barrett and Maingot to abandon anastomoses and cardioplasties. That same year, Wulff and Malm[176] of Lund, showed that of 6 Heller procedures, 4 had recurrences, due to inadequate short incisions and rows of superficial stitches in the serosa over the bulging mucosa. Three later patients, operated upon more adequately, did well. Of 18 patients who had cardioplasties, 7 had developed anemia, necessitating occasional transfusions. In 1956, Gammelgaard,[40] of Copenhagen, confirmed the trend toward the Heller procedure, which he performed generally through a left thoracic approach. This author, like others, warns against short incisions, and states that analysis of 5 poor results showed technical errors, or new esophageal conditions, such as diverticulum and hiatal hernia.

The most general early popularity of the Heller procedure was enjoyed in Holland, France, and Italy. In Holland, Zaaijer[178] recommended it in 1919, and reported 8 cases without any mortality in 1923.[177] At the International Congress of Surgery in Madrid in 1932[180] he stated that de Bruine Groeneveldt[15] modified the classical anterior and posterior incisions of Heller to a single anterior incision. Pieri[118] in Italy recommended the Heller procedure, and published 5 cases with good results in 1937. Marinacci[94] stated, in 1939, that the improvement after a Heller operation is startling.

The French surgeons have probably contributed more than any other group to the development of this special field of operative surgery and the Heller procedure. Their part is well described in the thesis by Latreille[83] from Santy's department at Lyon. After some early aberrations, such as the pulling down of the terminal esophagus with fixation around the diaphragmatic hiatus and cardioplasty by Sencert and Simon, Delbert introduced Heller's technique in France in 1929.[83] Since then large series have been accumulated in various French hospital centers. Santy[139-141] reported 94 cases in 1949, and 168 cases in 1956 (of 175 cases of achalasia), with 90 per cent over-all improvement and 6 postoperative deaths, of which 4 had peritonitis or mediastinitis, and 2 were bad-risk patients. Frank failures of the procedure were observed in 7.5 per cent of cases, due to various causes. Santy prefers the abdominal approach, with freeing up of the cardia and lower esophagus, and an anterior incision of approximately 10 cm. Careful hemostasis is of the utmost importance. In 146 operations, 8 had been done through the chest in 1954.[83] Santy does not think a double myotomy to be essential. According to him, there are four factors which influence the results of the Heller procedure in general: (1) age, (2) duration of the disease, (3) anatomic form of the disease, and (4) presence or absence of periesophageal inflammation. The younger the patient, and the

more recent his troubles are, the better a result can be expected. Huge dilatations and periesophageal inflammation yield more failures. Of 10 cases with severe inflammation, 7 were failures. One reason for persistent symptomatology after the operation is the presence of a diverticulum. Santy had 3 such cases, of which 2 were not recognized at the time of the Heller procedure.

De Gaudart d'Allaines and his pupil, Lortat-Jacob, also have come to accept the superiority of the Heller procedure, after some early misfortunes. D'Allaines[41] uses the abdominal approach and, after completion of the esophageal incision, fixes the esophagus to the gastric fundus. In case of a recurrence, the author prefers a thoracic approach. Lortat-Jacob[87-90] also observed the occurrence of esophagitis in anastomotic procedure. He therefore performs the Heller procedure (longitudinal myomectomy of 1 cm. width) and repairs the esophageal hiatus and reconstructs the angle of His, restoring the obliquity of the esophageal entrance into the stomach (esophagocardiogastropexy). This author also reserves the thoracic approach for recurrences after the Heller procedure, or if there is an associated disease of the thoracic esophagus. If a Heller procedure fails, dilatation and splanchnic infiltration should be attempted first. Lortat-Jacob does not see any advantage in a primary thoracic approach, except for the afore-mentioned special situation. Since there is also an alkaline reflux esophagitis, vagotomy in order to diminish the gastric acidity is not indicated.

At the Convention of French Surgeons in 1956, Fontaine[29, 30] of Strasbourg reported 14 cases with no mortality and 11 excellent-to-good results. He prefers a thoracic approach with a left splanchnicectomy from D_6 down to the diaphragm. He also makes a very long myotomy, extending from the fundus to the arch of the aorta. Welti, too, advocates the thoracic approach,[170-172] because it permits a better technical performance of the Heller procedure, allows recognition of multiple stenoses, and offers a better approach to the diaphragmatic hiatus. Chalnot of Nancy also gives his support to the Heller procedure.[20]

In the English-speaking countries, particularly in the United States, surgery in the treatment of achalasia had a slow start. C. E. Bird[14] thought in 1939 that this might be due in part to the fact that dilatation was used more persistently and with more success here than elsewhere (Vinson[160]). Berg[12] of New York is credited by Zaaijer[180] with having performed the first Heller procedure in the U.S.A. in 1918. We were unable to confirm Zaaijer's statement.[85] Scrimger[146] reported 2 Heller procedures in 1931, in the *Annals of Surgery*. One patient died of mediastinitis; the lumen had been entered during operation.

In their exhaustive paper, in 1940, Ochsner[112] and De Bakey collected 88 cases of esophagogastrostomies, with 5 deaths (6.6 per cent) and one poor result. They added 3 cases of their own, in which they had obtained good results. There were also 36 cardioplasties, with one death and one recurrence. These results appeared favorable as compared to the 104 cardiomyotomies collected from the foreign literature showing 4 deaths and 14 recurrences. They had also collected 80 cases of instrumental dilatation, with 7 deaths (8.9 per cent) and 8 failures (10.1 per cent). At that time the esophagogastrostomy appeared to

them the most rational procedure. Esophagitis was not discussed. In 1935, Churchill[21] reported briefly 2 esophagogastrostomies with preliminary left phrenic crush.

As anesthesia and postoperative therapy were improved, anastomotic procedures were considered the techniques of choice.[22, 145]

In 1949 appeared the first warnings of the dangers of esophagitis by Allison[3, 4] and Barrett.[9] The latter had performed both the cardioplasty and the esophagogastrostomy at the price of severe postoperative esophagitis, peptic ulcerations, and hemorrhage.

Suddenly the Heller procedure was re-discovered everywhere. Sweet noticed in 1947[153] that up to that time the Heller technique had not been used at the Massachusetts General Hospital, and that only 21 reports were found of it in the American literature. Since 1956 Sweet[151, 154] has been classifying achalasia into two morphologic groups: (1) large esophagus with stenotic atrophic distal segment (75 per cent) for which he performs a cardioplasty, and (2) moderately large esophagus with hypertrophic distal segment (25 per cent) for which he performs a cardiomyotomy.

In a group of 9 patients, with postoperative upper gastrointestinal bleeding, 5 patients had demonstrable pylorospasm.

Following the rediscovery, Kay[72] wondered "why this brilliant result (Heller's first), did not cause the operation to become generally more popular," and Hawthorne and Nemir[53] reviewed the major series of the English-speaking countries and their own, and also attested to the superiority of the Heller procedure.[109] By 1956, Hawthorne and associates[54] had treated 35 patients with a cardiomyotomy.

Heller has, at all times, used the technique as originally described in 1914. Special attention should be given to the double incision, since anterior incisions alone are certainly responsible for some of the poor results. Recurrence after double section of the muscularis has not been observed. Accidental opening of the esophageal mucosa is an obvious hazard, but in Heller's series, there have been no operative deaths.[60]

At present, the indications for cardiomyotomy are as follows: Early cases should be treated with the dilator. If several dilatations fail, operation should be performed. A primary operation should be done in advanced cases, with elongation and tortuosity of the esophagus, because of the danger of perforation with the dilator. Primary operation is indicated in patients who cannot be kept under observation, or who would find it difficult to return for repeated treatments.

The reasons his technique failed to attain the popularity of some of the other procedures in Germany, Heller attributes to the facts that many cases are cured by dilatation alone, but also that some of the authoritative masters of German surgery preferred the esophagogastric anastomoses. Since the second World War, with the very great advance of anesthesia and thoracic surgery, it appears to Heller that some surgeons prefer extensive and spectacular operations to the simple, though well-established techniques. Heller rejects the thoracic approach because it exposes the patient to a "Zweihöhlenoperation"

(abdomen and chest) which is completely unnecessary, since the myotomy can be easily done through the abdomen alone. He decries anastomoses because these incur the risk of infection, require unnecessary esophageal suturing, and invite reflux esophagitis and spur formation. The latter may be circumvented by crushing the spur, but this constitutes a "formidable" procedure. As to Wangensteen's procedure, Heller wonders what its rationale is. He had the opportunity to see such a patient who had developed scarring and stricture of the anastomotic site, with severe dilatation of the upper esophagus. The patient was in much worse condition than before operation. (Dr. Wangensteen,[168] himself, has condemned his extensive operation and has returned to a modified Heller procedure in which he uses a Foley catheter in order better to expose all the muscle fibers.)

Heller also agrees the the name "cardiospasm" is a poor term, and that "achalasia" is a better name. He compares the muscle of the cardia to those of the bladder neck and the anus. At rest these muscles are contracted, whereas, during the active phase, they become relaxed. During achalasia this relaxation does not occur, and in addition to this, the muscles of the upper esophagus are atonic when they should contract and propel food on. Since the operation is only directed at the cardia, nothing is done, nor can be done, for the musculature of the esophagus. Therefore, the dilatation of the upper esophagus persists, and food descends only because of its weight. This has been interpreted by some as a failure, when it really is not.

As to why the Heller procedure failed to gain general early recognition, a review of the literature does not yield a single technical or historical reason which could, of itself, explain the relative eclipse of the procedure. In addition to this, it must be remembered that the procedure experienced an early, if not immediate, popularity in the Latin countries (as contradictory as this may sound, if one thinks of the language difficulties and the poor cultural exchanges these parts of Europe experienced with Germany at the time of the creation of the procedure), in Holland and Scandinavia. Therefore, our remarks should probably be limited to the English-speaking countries and to Germany.

One of the major reasons for rejection of the Heller procedure was, and still is, the fact that the surgeons were treating the postoperative roentgenogram rather than the patients' symptoms, and that those who were opposed to the procedure, were so, in part, because of the observed persistence of a dilated esophagus. This ignores the rationale of cardiomyotomy which is an operation directed at the cardia, and not at the atonic esophagus. Actually, neither cardioplasty nor esophagogastrostomy ordinarily affects the dilatation. It has, in any case, been established that the radiologic dilatation is unrelated to the presence or absence of postoperative difficulties.

Some opponents also advanced the idea that the procedure itself might be dangerous, because of danger of perforation of the mucosa during the myotomy.[116] This is a reflection more on the technical skill of the performing surgeon than upon the rationale of the operation. Hesse[64] also mentions secondary rupture and "Durchwanderungsperitonitis" as one of the complications of Heller's procedure. It would be difficult to prove that the so-called secondary

ruptures are not really overlooked perforations at the time of operation, since such secondary ruptures have not been reported in the rather large series of some of the workers in this field. As to the peritonitis by permeation of the demuscularized bowel, this is a purely theoretical consideration, once raised also for the Fredet-Ramstedt procedure.

A third argument against the Heller procedure is that of the so-called recurrences. These are due mainly to periesophageal scarring and constriction, secondary to the dissection in that region. As Santy states, many of these can be prevented by gentle technique and very careful hemostasis. Some of the recurrences in early times were also due to the fact that the myotomy was not generous enough, and/or that a double incision should have been done. If a recurrence occurs, it can be taken care of in most instances by postoperative dilatations, and this should be first attempted in all such instances before more formal procedures.

Although the Heller procedure is the most anatomic technique of all those which have been proposed, subsequent reflux may occur, and has been reported by certain authors, especially if the patient is in dorsal decubitus. Esophagitis has been reported in such cases, as Lortat-Jacob and Allison point out. This is almost certain to be due to an esophageal hiatal hernia, either pre-existing, or due to the operative manipulations during performance of the Heller procedure. For this reason, reconstruction of the angle of His (Lortat-Jacob, Santy, d'Allaines) and a reconstruction of the esophageal hiatus (Allison, Santy, Lortat-Jacob) are indicated, and probably should be done routinely.

The coexistence of pylorospasm and achalasia has been described by several authors. The pylorospasm, if missed, might create difficulties after operation. Here again the argument applies equally to other operative measures for achalasia. Hawthorne and Nemir have recently attempted performance of a pyloroplasty at the time of the Heller procedure, but did not think this to be advantageous.

Finally, it is clear that postoperative esophagitis after anastomotic procedures was the determining factor leading to the "come-back" of the Heller procedure. This complication must have been poorly understood at the outset of esophageal surgery, and was recognized only as surgery for benign conditions of the cardia with the severe modification in the normal anatomy developed.

The Heller procedure appears to be the safest and most effective operative treatment of achalasia. The mechanism of function of this rather empirical technique is unknown. The best explanation for the success of the cardiomyotomy is the fact that, in relieving what is in effect an obstruction, the operation disturbs minimally the normal anatomy of the cardia, and does not create any new pathophysiologic processes. The operation should be supplemented by additional steps in technique. We think that the abdominal approach is the more rational one in cases where the barium swallow does not reveal any spastic contractions of the higher levels of the esophagus. Reconstruction of the angle of His, and of the esophageal hiatus will prevent the occasional case of postoperative esophagitis. While the double myotomy of Heller would make assurance doubly sure, it would not appear to be necessary in most cases.

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